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Pituitary Somatostatin Receptor Signaling

Anat Ben-Shlomo and **Shlomo Melmed**
Pituitary Center, Department of Medicine, Cedars Sinai Medical Center, Los Angeles, California 90048

Abstract

Somatostatin (SRIF) is a major regulator of pituitary function, mostly inhibiting hormone secretion and to a lesser extent pituitary cell growth. Five SRIF receptor subtypes (SSTR1–5) are ubiquitously expressed G-protein coupled receptors. In the pituitary, SSTR1, SSTR2, SSTR3 and SSTR5 are expressed, with SSTR2 and SSTR5 predominating. As new SRIF-analogs have recently been introduced for treatment of pituitary disease, we evaluate the current knowledge of cell-specific pituitary SRIF receptor signaling and highlight areas of future research for comprehensive understanding of these mechanisms. Elucidating pituitary SRIF receptor signaling enables understanding of pituitary hormone secretion and cell growth, and also points to future therapeutic development for pituitary disorders.

Keywords

somatostatin receptors; pituitary

Somatotropin-release inhibitory factors (SRIF) or somatostatins are cyclic peptides cleaved from a precursor pre-pro-somatostatin peptide to produce two bioactive products SRIF14 (14 amino acids) and SRIF28 which comprises an additional 14 N-terminal amino acids [1]. SRIFs are phylogenetically ancient, as SRIF-like immunoreactivity is found in protozoans, primitive intervertebrates and vertebrates [1,2]. SRIFs are produced from specialized cells in the brain, gastrointestinal tract (GIT), liver, pancreas, lungs, immune system, kidneys, adrenals and urogenital tracts [1]. SRIF exerts broad, mostly inhibitory effects on endocrine and exocrine secretions. Other than pituitary hormones discussed in this review, SRIF also inhibits secretion of gastro intestinal tract (GIT) hormones including insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide and secretin. SRIF also inhibits exocrine gastric acid, pepsin, pancreatic enzymes, bile and intestinal fluids secretions [3]. SRIF inhibits gastric emptying, gallbladder contraction, and small intestine segmentation, but inducess migrating motor complex activity and splanchnic vasoconstriction [1]. Brain SRIF inhibits release of hypothalamic hormones including corticotropin releasing hormone (CRH), thyrotropin releasing hormone (TRH), and also dopamine and norepinephrine [1].

Hypothalamic SRIF is a major regulator of pituitary gland hormone secretion and to a lesser extent, pituitary cell development and growth. The peptide is produced predominantly in the

Correspondence: Shlomo Melmed, M.D., Cedars-Sinai Medical Center, 8700 Beverly Blvd., Academic Affairs, Room:2015, Los Angeles, CA 90048, USA, Tel: 310-423-4691, Fax: 310-423-0119.

anterior periventricular nucleus, as well as in paraventricular, arcuate and ventromedial hypothalamic nuclei. These neurons project to the median eminence from which SRIF is secreted into the adenohypophyseal portal vein system to impinge on anterior pituitary cells [1]. Some neuronal axons course through the neural pituitary stalk and terminate directly in the posterior pituitary [4]. Other less prominent routes for SRIF to reach the pituitary include "leakage" directly from the 3rd ventricle to the portal system, peripheral SRIF derived mostly from the gut, and circulating blood crossing from the posterior to the anterior pituitary [4]. Thus SRIF acts as an endocrine hormone at the anterior and posterior pituitary [1]. Although paracrine SRIF action was suggested to occur within GH-secreting ademonas [5], *SRIF* mRNA has not been found in other pituitary tumor types or in fetal pituitary glands [5]. Compelling evidence for paracrine pituitary SRIF action is yet to be shown.

The five SRIF receptor subtypes, SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5, are seven-transmembrane domain guanine nucleotide-binding protein (G-protein) coupled receptors that bind endogenous SRIF receptor (SSTR) ligands, including SRIF and cortistatin [1]. These receptors are ubiquitously and differentially expressed in SRIF producing organs mentioned above, and also in blood vessels, muscle, cartilage, bone and abundantly in the pituitary [1].

Released SRIF is rapidly inactivated by tissue and blood peptidases, and the very short half-life (~ 2 minutes) limits its therapeutic use. Octreotide and lanreotide are clinically approved metabolically stable SRIF agonists with high affinity to SSTR2 and lower affinity for SSTR5 [6]. Pasireotide, binds SSTR5 > SSTR2 > SSTR3 > SSTR1 and is currently in clinical trials [7]. BIM-23A760, a chimeric compound, binds SSTR2 > SSTR5 and also binds the dopamine receptor subtype 2 (D2R) [8] and is currently in clinical trials. BIM-23120, BIM-23206 and BIM-23268 are experimental SRIF mono-receptor agonists with unique selectivity to single SRIF receptor subtypes [9,10].Ligand binding affinities to SRIF receptor subtypes are depicted in Table 1. Importantly, binding affinities were determined in isolated cell membranes derived from chinese hamster ovary (CHO), human embryonic kidney (HEK293) or cercopithecus aethiops (COS7) cells over-expressing a single receptor subtype. These systems might be biased by changes of receptor configuration at rest due to membrane isolation techniques, differences in submembranal pathways from natural pituitary cell targets, and receptor subtype interaction that is unapparent in cells expressing only one respective receptor. Therefore, whole live-cell binding affinity in cells targeted for treatment expressing one or different combinations of SSTRs would be more favorable in vitro models for studying pituitary signaling.

Although previous reviews have comprehensively addressed general SRIF receptor signaling in different tissues, it has been over 20 years, prior to SRIF receptor subtype discovery, that pituitary SRIF receptor signaling has been reviewed [4]. Somatostatin agonists for treatment of acromegaly and Cushing's disease are currently entering clinical trials, e.g. Pasireotide, the multi-receptor ligand that more closely resembles endogenous SRIF14 binding characteristics than the clinically used octreotide and lanreotide, and the chimera BIM-23A760 that binds both D2R and SSTR2. As we now appreciate the contribution of cell specificity to SSTR signaling, it is important to distinguish pituitary somatostatin receptor signaling, and elucidate further pathways for study. This review focuses on pituitary SRIF receptor signaling and biological actions in this major SRIF target organ.

Pituitary SSTR expression

Summarizing knowledge on pituitary SSTR signaling is challenging as different cell models, species and techniques have been used to study small and very focused portions of complex SRIF signaling pathways. As most reports do not discriminate between different receptor subtypes, a comprehensive understanding of pituitary SSTR signaling has yet to emerge. The

most utilized models have been rat pituitary or human tumor cultures, and rodent cell-lines. AtT20 corticotroph cells were generated from anterior pituitary tumors in LAF_1 female mice that survived ionizing radiation, and secrete adrenocorticotropin hormone (ACTH) [11]. GH_3, GH_4C_1 and GC cells are female Wistar-Furth rat tumoral somatotroph cells secreting varying ratios of prolactin (PRL) and growth hormone (GH) [12,13]. TtT/GF mouse folliculo-stellate cells are non-endocrine anterior pituitary cells that support pituicytes, secrete cytokines and growth factors and exhibit scavenger activity [14]. SSTR expression profiles in these pituitary cell types are presented in Table 2.

All SSTRs are expressed in the human fetal pituitary, whereas the adult human pituitary expresses mainly SSTR1,2,3 & 5 (Table 2) [15]. Pituitary SSTR5 and SSTR2 are highly abundant in normal pituitary cells, whereas the other receptor subtypes are less markedly expressed (Table 2). In rodents, SSTR2 exists as two spliced variants, SSTR2a and SSTR2b, which differ at the C-terminus; however, the rodent pituitary expresses only SSTR2a. Humans express SSTR2a but not SSTR2b [1]. SSTR expression profiles in pituitary adenoma are presented in Table 3.

Multiple factors known to regulate pituitary SSTR gene expression are summarized in Table 4. Rat pituitary SSTR2 mRNA and protein levels increase immediately after birth and progressively with age in a SRIF-independent manner[16], and are higher in males than females [17]. Whether or not these changes are relevant to GH regulation is unclear. Most pituitary cells express more than one SRIF receptor subtype raising the possibility of membranal or sub-membranal physical dimerization which might alter pituitary cell responses to multi-receptor specific SRIF analogs. Even though evidence suggests that heterodimerization of receptor subtypes occurs within the SSTR family or with other receptors like D2R in non-pituitary cell-lines (CHO or HEK293) stably expressing exogenous receptors [18], there is as yet no evidence for receptor dimerization in pituitary cells. SSTR2 and SSTR5 synergize functionally to inhibit GHRH-induced GH secretion from primary human fetal pituitary cultures, using selective SSTR2 and SSTR5 agonists [19]. In addition, SSTR5 also regulates SSTR2 action in mouse pituitary corticotroph AtT20 cells, as a selective SSTR5 agonist attenuated SSTR2-selective agonist inhibition of calcium oscillations and SSTR2 internalization [9] [20]. It is not known whether SSTRs physically dimerize in pituitary cells, but the assumption of functional interaction between downstream receptor signaling pathways is reasonable and adds to the complexity of understanding SRIF action through canonical receptor subtypes.

Pituitary SSTRs also regulate downstream signal transduction in the absence of a specific ligand indicating that pituitary SSTR activity might in fact be a constitutive property [21,22]. Evidence supporting this observation is gleaned from experiments whereby knock-down of SSTR2, SSTR3 or SSTR5 levels increased baseline cAMP and ACTH levels in AtT20 cells, and of cAMP in pituitary folliculostellate cells. SSTR2, SSTR3 or SSTR5 over-expression also attenuated AtT20 cell responses to CRH through ligand-independent down-regulation of CRHR1 expression. The ability of SSTRs to regulate corticotroph cell ACTH secretion and response to other hormones in systems devoid of SRIF ligand is physiologically intriguing, as this observation implies that SRIF receptor subtypes might have a role in homeostatic SRIF-independent regulation of pituitary function. If proven in vivo, constitutive SSTR activity could alter our understanding of normal and disrupted pituitary function.

Pituitary signaling pathways regulated by somatostatin receptors

More than 20 intracellular SRIF signaling pathways have been described in non-pituitary cells [18]. Studies of pituitary SRIF signaling pathways have focused mostly on calcium and potassium channels and adenylyl cyclase-cAMP-PKA signaling with less emphasis on other pathways. Even though SSTR subtype structure is similar throughout the body, the ratios of

receptor subtype expression differ between different organs and cells, in changing cell environments and in submembranal signaling pathways. Therefore, the assumption that SRIF signaling through canonical receptors is similar in different cells is likely not absolute, and should be evaluated using cell specific/organ specific approaches.

In general, hormone secretion can be blocked acutely and/or chronically, by inhibition of mRNA transcription, protein synthesis and modification, hormone packaging, trafficking or exocytosis. Inhibition of cell growth can be mediated through cell cycle arrest, increased apoptosis or senescence. Accumulated knowledge of pituitary SRIF action for each of the above cell functions is summarized in Table 5.

Ion channel regulation

Hypothalamic hormones including GHRH [23], CRH [24], GnRH [25], TRH [26], and Activin A [27] regulate anterior pituitary hormone secretion by increasing intracellular Ca^{2+} levels and exocytosis. For example, GHRH opens tetrodotoxin-insensitive Na^+ channels causing membrane depolarization and an action potential burst which in turn increases Ca^{2+} transient frequency and intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) leading to enhanced hormone exocytosis [23]. SRIF antagonizes these effects causing membrane hyperpolarization by opening K^+ channels and decreasing Ca^{2+} transient frequency and $[Ca^{2+}]_i$, all resulting in decreased hormone exocytosis. SRIF activates inwardly rectifying K^+ (K_{ir}) channel conductance in GH_3 cells [23], stimulates large-conductance, calcium and voltage-activated K+ channels (BK) in GH_4C_1 cells [28], and activates K^+ influx through both K_{ir} and delayed rectifying K+ channels by stimulation of pituitary SSTR2 and SSTR4 [29,30]. These effects culminate in membrane hyperpolarization and closure of L-type voltage sensitive calcium channels (VSCC) and are abolished by pertussis toxin (PTX) pre-treatment, indicating $G\alpha_{i/0}$ unit mediated activity [23,24]. In AtT20 cells, SRIF-induced K^+ influx was regulated by $G\alpha_{i3}$ [31]. In somatotroph cells, G_{i3} mediates the SRIF effect on K^+ currents [32] and $G\alpha_{02}$ [32,33], β_1, β_3 [34] and γ_3 [35] mediate SRIF regulation of intracellular Ca^{2+} currents. In rat GH-secreting cells, SRIF action is primarily mediated via SSTR2, causing closure of L and N type but not T or P/Q type VSCC [36–38]. It is yet unclear whether SRIF affects Ca^{2+} channels independently from K^+ channels in pituitary cells. SRIF reduction of intracellular calcium acutely inhibits exocytosis of hormone containing vesicles [39–41]. Frequency and amplitude of calcium oscillations correlated directly with the amount of GH released from somatotrophs, whereas removal of extracellular calcium, calcium channel blockers and SRIF acutely suppressed calcium excursions [42]. SRIF treatment redistributed somatotroph cytoplasmic microfilaments without affecting intracellular GH content [43], and SRIF reduced association of Rab3B and SNARE exocytosis proteins [44]; both mechanisms are Ca^{2+} dependent. Therefore, K^+ derived membrane hyperpolarization and reduction in Ca^{2+} influx and $[Ca^{2+}]_i$ is a major mechanism by which SRIF acutely inhibits exocytosis of pituitary hormone containing granules. Further studies are needed to evaluate SRIF induced K^+/Ca^{2+} effects on pituitary cell growth.

Adenylyl cyclase-cAMP-PKA pathway

SRIF is a general inhibitor of the adenylyl cyclase-cAMP-PKA pathway. SRIF inhibited CRH, isoproterenol, vasoactive inhibitory peptide (VIP), forskolin and cholera toxin-induced cAMP accumulation and ACTH secretion from AtT20 cells [45] and GHRH-stimulated cAMP and GH from primary pituitary cultures [46]. SRIF inhibition of adenylyl cyclase is $G\alpha_{i/0}$ dependent as PTX attenuated SRIF inhibition of VIP-induced cAMP in GH_4C_1 cells [47], specifically through $G\alpha_{i2}$ [48]. In AtT20 cells, SRIF inhibited adenylyl cyclase and ACTH secretion through $G\alpha_{i1}$ [49]. SSTR1, 2, 3 and 5 are all involved in SRIF inhibition of adenylyl cyclase in pituitary cells. In GH_4 cells over-expressing SSTR2, SRIF inhibited forskolin-stimulated cAMP accumulation, PKA activation and cAMP response element-binding protein (CREB)

phosphorylation. PTX treatment as well as over-expression of the PKA catalytic subunit attenuated SRIF action [36]. SSTR2, SSTR3 and SSTR5 mediate AtT20 cell SRIF-inhibition of cAMP [9], and SSTR1 acts similarly in GC cells [50]. It is unknown whether reduced cAMP inhibits hormone secretion independently of Ca^{2+} inhibition, as both processes occur simultaneously after SRIF treatment; therefore, the relative contribution of this pathway to inhibition of pituitary secretion is unclear.

Even though SRIF action on adenylyl cyclase is mainly inhibitory, there is evidence suggesting that SRIF might exert a dual dose dependent effect on cAMP as observed in primary porcine somatotrophs where both low and high SRIF concentrations uniquely increased, rather than decreased, cAMP accumulation [51]. It is unclear which receptor subtype contributes to this phenomenon and by what mechanism. One possibility is that like other GPCRs, SSTRs might couple to either $G_{\alpha i/o}$ or $G_{\alpha s}$ depending on ligand binding and receptor conformation. Dual dose-dependent SRIF action on pituitary cells adds a further complexity to understanding SSTR signaling of pituitary SRIF agonist action.

Phosphoprotein phosphatase (PTP) pathway

Studies on SRIF effects on the PTP pathway have focused mainly on cell growth. SRIF increased tyrosine phosphatases and serine/threonine phosphatase activity in non-functioning human pituitary tumors, GH-secreting adenoma cells and in GH_4C_1 cells [18]. A recent review analyzed SRIF activation of the PTP pathway [52]. SRIF inhibition of phorbol ester-stimulated DNA synthesis was blocked by vanadate, a tyrosine phosphatase inhibitor [52]. In GH_3 cells, octreotide exhibited an antiproliferative effect blocked by knockdown of Zac1, a tumor suppressor gene that causes cell cycle arrest and apoptosis. This antiproliferative effect of octreotide was due to PTX-dependent tyrosine dephosphorylation of the PI3K/Akt survival pathway which led to Zac1 up-regulation [52]. In patients with acromegaly treated with octreotide, strong ZAC1 immunoreactivity correlated with IGF-1 normalization and tumor shrinkage [52]. In cultured human GH-secreting adenomas, BIM23120, a SSTR2 selective agonist, dose-dependently induced apoptosis that was blocked by a phosphatase inhibitor [52]. As PTP activity is important for GPCR regulation of cell growth arrest [52], SRIF regulation of this pathway in mediating pituitary growth should be studied more rigorously; moreover, the role of SSTRs other than SSTR2 should be evaluated.

Few other signaling pathways have shown to be involved in pituitary SRIF action [18], including PKC, guanylyl cyclase and nitric oxide (NO), mitogen-activated protein kinase (MAPK) and PI3K/Akt. However, as yet, specific physiological relevance of these pathways to pituitary cell function is unclear. SRIF inhibited both PKC stimulation of GH secretion [53] and NO-induced cGMP and GH levels [54,55]. As shown for dual SRIF activation of adenylyl cyclase, SRIF also exhibits a biphasic dose-dependent pattern on pituitary guanylyl cyclase regulation and cGMP accumulation [56], supporting the dual action theory. SRIF blocked phospholipase A2-mediated GHRH and TRH induced pituitary arachidonate release [57] and decreased arachidonate levels in GC cells [58].

SRIF effects on MAPK pathways are unclear, as reports have been conflicting. Octreotide and pasireotide decreased MAPK/ERK phosphorylation in both GH_3 cells and in GH-secreting adenoma cultures, whereas SSTR5 knockdown increased AtT20 ERK phosphorylation [21]. In contrast, another study found that octreotide activated PI3K/Akt survival and MAPK pathways through SSTR2 and SSTR5 in GH-secreting cells, to induce histone methyltransferases associated with menin, that in turn induced p27(Kip1) to promote cell growth arrest [59]. It is unclear whether these discrepancies exemplify dual SRIF action or whether they reflect cell-specificity of SSTR profiles or downstream signaling pathways. It is apparent that knowledge of phosphatase and kinase involvement in pituitary SRIF effects is limited and requires further investigation.

Receptor phosphorylation, internalization and desensitization

As for other GPCRs, SSTR phosphorylation and internalization lead to receptor desensitization and attenuated receptor related signaling. This is a crucial feedback mechanism that prevents persistent stimulation by the agonist. Of all SSTRs, SSTR2 is the only receptor subtype to exhibit this sequence of events, as SSTR1 was shown not to internalize [60], whereas SSTR5 reports are contradictory and other receptor subtypes have not been studied in pituitary cells. SSTR2 is acutely phosphorylated and internalizes upon SRIF and SSTR2-selective agonist treatment, and pituitary binding sites are acutely down-regulated in GH4C1 cells stably over-expressing SSTR2 [61]. SRIF increases SSTR2 phosphorylation on five C-terminal serine and threonine residues [62]. In contrast to SSTR2, studies on SSTR5 are conflicting. In GH_3 cells, the third hSSTR5 intracellular loop was shown to be important for receptor phosphorylation and internalization followed β arrestin 2 binding [63]; however, in AtT20 transfectants, hSSTR5 did not internalize upon SRIF or SSTR5-selective agonist treatment [9,60]. Moreover, SSTR5-selective agonists and pasireotide did not acutely downregulate SSTR5 [10,64] raising the possibility that SSTR5 remains active in the membrane longer than SSTR2, allowing further receptor activation and signaling.

SSTR2 internalization is followed by receptor desensitization. Prolonged SRIF treatment (> 1 hour) induces AtT20 and GH_4C_1 desensitization [61], decreasing responses to SRIF inhibition of cAMP, in addition to enhancing forskolin, CRH, VIP, and isoproterenol induction of adenylyl cyclase and cAMP [64–66]. In mono-receptor AtT20 transfectants, most observed SRIF desensitization was regulated through SSTR2 and not SSTR5, consistent with the observed absent visualized SSTR5 internalization in these cells [64]. *In vitro* studies might not reflect pituitary receptor behavior *in vivo*, and it is hard to predict *in vivo* patterns of SSTR2 internalization and desensitization. Whether SSTR5 and SSTR1 internalize or not *in vivo* and/or exhibit pituitary cell-specific trafficking characteristics requires further study.

Physiological effects of SRIF receptor signaling

The dominant effect of SRIF on pituitary function is inhibition of hormone secretion mostly due to acute inhibition of hormone exocytosis. Inhibition of hormone synthesis has not conclusively been proven. Whereas some studies showed decrease in somatotroph GH mRNA levels [67–69], others showed no change [70–74] or even an increase, likely reflecting rebound GH synthesis after cessation of SRIF treatment, underlying the importance of timing of SRIF effects. Secondary effects of SRIF include inhibition of cell growth. There is as yet uncertainty as to whether this effect derives from inhibition of cell proliferation, induction of cell apoptosis or induction of cell senescence.

Inhibition of pituitary tumor hormone secretion and cell growth is usually synchronous as tumors responding to SRIF agonists with GH inhibition also exhibit some tumor shrinkage. However, rarely are there cases in which these functions are asynchronous, and tumor shrinkage is not accompanied by inhibition of hormone secretion [75]. In one tumor, SSTR5 levels were higher than SSTR2, suggesting that SSTR5 might mediate anti-proliferative effects whereas SSTR2 mediates the anti-secretory effect [76]. Studying these tumor types might help unravel differences in SSTR specific signaling pathways and should be further explored.

Growth inhibition

SRIF inhibition of cell growth was demonstrated in normal and tumoral pituitary cells *in vivo*. Acute central SRIF administration directly into rat brain ventricles inhibits somatotroph, lactotroph [77], LH-secreting gonadotroph [78] and thyrotroph [79] proliferation. In adrenalectomized rats that have higher CRH levels due to lack of glucocorticoid negative feedback, both octreotide and pasireotide inhibited increased pituitary mitotic activity [80]. In

all studies, it is unclear whether the SRIF anti-growth effect is mediated through inhibition of specific hypothalamic releasing factors or whether it is a direct effect on pituitary cells.

SRIF does not impact mitogenesis in mouse pituitary models. In fact, pituitary volume is not altered in SRIF null mice [81,82]; moreover, somatotroph hyperplasia or adenoma formation was not observed in these mice for up to 2 years, indicating that SRIF does not significantly prevent pituitary trophic activity. GHRH, on the other hand, stimulates somatotroph cell proliferation; however, when GH cells are chronically stimulated by GHRH in SRIF null mice cross-bred with transgenic mice over-expressing GHRH, pituitary volume was 25% larger than in control mice over-expressing only GHRH. This effect was shown to occur independently of cell proliferation, supporting mechanisms including senescence or apoptosis [82] rather than inhibition of mitogenesis. Another example for SRIF's inability to control cell mitosis are null mice mutants for the glycoprotein hormone alpha-subunit ($\alpha GSU^{-/-}$). These mice have TSH deficiency and hypothyroidism and are expected to have increased TRH levels. SRIF was shown to inhibit TSH through SSTR2; however, compound double transgenic $SSTR2^{-/-}$ $\alpha GSU^{-/-}$ knockout mice developed thyrotroph hyperplasia, similar to $\alpha GSU^{-/-}$ mutants, indicating that SSTR2 does not protect the pituitary from increased thyrotroph cell proliferation. However, SRIF effects on apoptosis or senescence in this model were not evaluated [83]. In contrast, the SSTR2 agonists lanreotide and octreotide prevented exogenous estradiol [84] or its agonist diethylstilbestrol (DES) [85], respectively, from inducing pituitary hyperplasia and prolactin (PRL) hypersecretion in female rats. The latter study also found BrdU incorporation to be reduced by octreotide; however, a clear distinction between cell proliferation and cell apoptosis was not reported. Another physiological cause for lactotroph hyperplasia is pregnancy; however, evaluation of SRIF effects on pituitary cells during pregnancy has not been reported. SRIF effects on mitosis in these models are also unclear, whereas direct SRIF effects on apoptosis and senescence could be of consequence and require further study.

Human studies show shrinkage of GH and TSH secreting pituitary adenomas with octreotide and lanreotide [86]. In two critical reviews evaluating pituitary GH-secreting tumor shrinkage in patients receiving octreotide or lanreotide, ~50% of patients showed tumor size reduction especially in those receiving primary pharmacotherapy. Mean tumor size reduction was ~50% with a large range of responses. Moreover, 97% of patients exhibited control of tumor growth [87,88]. Although octreotide treatment did not affect growth of ACTH-secreting pituitary adenomas in Cushing's disease, octreotide inhibited further growth of Nelson's tumor associated with post-adrenalectomy growth of an ACTH-secreting adenoma [89]. Octreotide treatment also reduced TSH-secreting adenoma size in one third of patients [90], but had no effect on the sizes of prolactinoma or non-functioning pituitary tumors [75]. Mechanisms responsible for tumor growth arrest or shrinkage were shown to be mediated by both SSTR2 and SSTR5. In somatotroph tumor cell cultures, both SSTR5 andSSTR2 signaling increased p27 and decreased cyclin D1 levels indicating growth arrest, but only SSTR2 activation induced cell apoptosis in a phosphatase-dependent way [91]. SRIF and lanreotide inhibited phorbol myristate acetate (PMA)-induced [^{3}H]Thymidine uptake and cell proliferation in primary non-functioning pituitary tumor cultured cells [92]. In GH-secreting adenoma or prolactinoma cultures, over-expression of adenoviral-linked SSTR2 increased apoptosis and decreased cell viability [69]. Pasireotide, a multi-receptor SRIF analog with high affinity to SSTR5, reduced the number of viable cells by up to 70% in cultured ACTH-secreting tumors [93]. These studies indicate that SRIF might exhibit pro-apoptotic rather than anti-mitogenic effects on pituitary tumor cells, supporting the results obtained in animal models described above. However, some studies have not shown increased apoptosis; for example, GH-secreting adenomas derived from patients pre-treated with octreotide for 3 months prior to transsphenoidal surgery exhibited reductions in both cell proliferation (Ki-67) and apoptosis [94]. SRIF14 and octreotide both exhibited a cytostatic effect on GH_3 cells partially inhibiting cell cycle progression from G_0/

G_1 to S phase with no apoptosis [95], findings that might indicate premature cell cycle arrest and increased cell senescence. Taken together, these studies suggest that SRIF effects on pituitary cells are either pro-apoptotic or pro-senescent rather than anti-mitogenic.

Hormone secretion

GH secretion—The dominant function of SRIF is to inhibit hormone secretion, in particular that of GH [96]. Animal and human studies demonstrate SRIF to be a major inhibitor of basal and GHRH-induced GH secretion [4], in addition to direct inhibition of hypothalamic GHRH secretion [97]. Central SRIF-regulating factors alter SRIF release from the hypothalamus, thereby regulating pituitary GH secretion. These factors include serum GH/IGF-1, exercise and immobilization that increase SRIF release, whereas high glucose levels in humans inhibit SRIF release [96].

As SRIF inhibitory effect on GHRH-stimulation is substantial [96], SRIF null mice were expected to have high levels of GH and IGF-1; however, even though GH levels were moderately increased, body lengths were not different from WT [81,98], and IGF-1 levels were unchanged [81] but moderately elevated in another study [98]. These results imply that whereas SRIF is an important inhibitor of GHRH action, the peptide plays a less prominent role in maintaining baseline GH secretion from the pituitary.

The role of each SSTR subtype in SRIF inhibition of GH secretion is not yet fully apparent. SSTR2, SSTR5 and to some extent SSTR1 play important roles in somatotroph GH inhibition. In the normal fetal pituitary (gestation weeks 18–30), co-treatment with SSTR2 and SSTR5 selective agonists inhibited GHRH-stimulated GH secretion more effectively (73%) than each agonist separately (32 and 34%, respectively) [19] and at 25 weeks gestation, both SSTR2 and SSTR5 agonists inhibited GH secretion [99]. Octreotide and lanreotide both activate SSTR2 and to a lesser extent SSTR5. These two SRIF analogs are currently utilized for treating GH-secreting adenomas. Approximately 70% of patients harboring pituitary GH-secreting adenomas exhibit reduced serum GH levels and normalized serum IGF-1 levels with these drugs [86]. Increased somatotroph SSTR2 density enhances sensitivity to SSTR2-selective ligands like octreotide [69,100]. Furthermore, an experimental compound with high affinity to both SSTR2 and SSTR5 was 40% more effective in suppressing GH in GH-secreting adenoma cultures than either octreotide or lanreotide or a selective SST5 agonist alone [101], supporting a functional interaction between the two receptor subtypes. SSTR1 was also shown to regulate GH secretion from these tumors, as an SSTR1 selective agonist reduced GH secretion in tumor cultures [102] and in GC cells [37]. Pasireotide which binds all three receptor subtypes (SSTR5 > SSTR2 > SSTR1) was more effective in long term reduction of serum GH levels than octreotide in animal models; however, its advantage over octreotide which activates SSTR2 > SSTR5 but not SSTR1 in GH-secreting adenomas is yet unproven [103] and currently in clinical trials.

ACTH secretion—The precise role of SRIF in pituitary ACTH secretion regulation has yet to be clarified [104]. SRIF infusion did not affect basal or acutely stimulated ACTH or cortisol levels in humans, and neither octreotide nor lanreotide, both SSTR2-selective agonists, were effective in treating ACTH-secreting pituitary adenomas causing Cushing's disease [104]. In contrast, SRIF, octreotide and pasireotide partially inhibited CRH-induced ACTH and cortisol secretion in pituitaries derived from long-term adrenalectomized rats or in serum deprived pituitary cultures [104]. Pasireotide, by preferentially affecting SSTR5 activity, inhibited ACTH secretion in five of six ACTH tumor cultures [93]. This discrepancy was explained by the presence of high circulating glucocorticoids that down-regulate corticotroph cell SSTR2 expression, as pituitary corticotroph cells were sensitized to octreotide in a serum-free environment or after treatment with glucocorticoid receptor blockade (RU-38146) [104].

Moreover, in the absence of circulating cortisol levels, as observed in patients with adrenal insufficiency or Nelson's tumor, octreotide effectively inhibited ACTH secretion [104]. In addition, pasireotide was recently shown in a phase 3 clinical trial to suppress urinary free cortisol levels in some patients with Cushing's disease [105]. The beneficial effect of pasireotide might be attributed to the fact that corticotroph SSTR5 expression which exceeds that of SSTR2, is not down-regulated by glucocorticoids [10] and perhaps does not internalize [9]. Strong evidence for SRIF and SSTR5 involvement in corticotroph cell secretion is derived from SRIF null mice and SSTR5 null mice models, both which exhibit high ACTH and cortisol levels at baseline [104]. Taken together, SRIF appears to be a regulator of corticotroph ACTH secretion. Whereas SRIF and SSTR2 agonist inhibition of ACTH secretion depends on circulating serum cortisol level and membrane SSTR2 density, SSTR5 agonist inhibition of ACTH secretion is not dependent on cortisol levels or SSTR5 density.

TSH secretion—SRIF inhibits basal and TRH-stimulated TSH secretion; however, thyrotrophs are less sensitive to SRIF action as compared to somatotrophs [4]. Both SSTR2 and SSTR5 were implicated in suppressing TSH secretion [99]. In healthy volunteers, SRIF suppressed TSH pulse amplitude and frequency [106] and inhibited TSH levels in normal subjects and in patients with primary hypothyroidism [2]. Octreotide and lanreotide reduced TSH secretion and normalized FT_4 and FT_3 levels in 90% of patients harboring pituitary TSH-secreting adenomas [90]. As TSH secreting adenomas are extremely rare, patient and tissue availability limit more extensive studies.

Prolactin secretion—SRIF effects on normal lactotroph PRL secretion are modest [2], and human prolactinomas are not sensitive to octreotide [8]. However, activation of SSTR5, abundantly expressed in human prolactinomas, inhibits prolactin secretion [101,107]. In fact, SRIF inhibition of PRL secretion might be estrogen dependent. PRL secretion in female rat pituitary cell cultures treated with 17β estradiol was more sensitive to SRIF and octreotide than untreated cells. Also, female rats receiving 17β estradiol exhibited reduced PRL secretion when treated with lanreotide [84]. This might be explained by increased SSTR2 and SSTR3 mRNA expression observed with 17β estradiol treatment [108]. Male rat lactotroph primary cultures do not exhibit SRIF-inhibition of PRL secretion, but in fact gain SRIF sensitivity after 17β estradiol treatment [109,110]. Moreover, SRIF inhibits estrogen-mediated PRL increase in men (male-to-female transsexuals), and to a greater degree in men treated with both estrogen and cyproterone acetate [111]. SRIF inhibition of basal PRL secretion becomes important in the presence of an estrogen surge in both men and women. As estrogen increases SRIF transcription [96], it would be interesting to study estrogen-SRIF interactions during and after pregnancy.

Gonadotropin secretion—Current knowledge of SRIF regulation of LH and FSH is limited. In healthy volunteers, SRIF inhibited LH pulse amplitude but not frequency, without affecting FSH pulsatility [106]. SRIF suppressed gonadotropin levels in 60% of FSH-producing pituitary tumors and 30% of LH-secreting pituitary adenoma cultures [112]; however, as most LH and FSH secreting adenomas are clinically non-functioning, measuring LH and FSH secretion is not clinically relevant.

In summary, SRIF is a major regulator of baseline and stimulated hormone secretion in the normal and tumoral pituitary. GH and TRH are predominantly regulated through SSTR2, whereas ACTH and estrogen-induced PRL appear to be regulated mostly through SSTR5. Receptor subtype abundance on the membrane of different pituitary cell types generally correlates with hormone action. Additional SSTR subtypes might be involved in hormone secretion and require further study.

Summary

Comprehensive understanding of pituitary SSTR signaling remains challenging. The most studied pathways in pituitary SRIF receptor signaling are regulation of intracellular calcium concentration and adenylyl cyclase activity, and the most abundantly expressed pituitary SSTRs are SSTR5 and SSTR2. Studies to date have focused on agonistic effects of these receptors, examining signaling upon stimulation with an agonist. Yet, these receptors, like other GPCRs, likely exhibit constitutive activity, as shown *in vitro*, highlighting the potential for studying inverse agonistic SSTR effects. Nevertheless, several significant technical challenges face the study of pituitary SRIF receptor signaling (Box 1). Efficient isolation of specific pituitary cell types should enable study of SRIF receptor profiles and selective signaling functions. Ultimately, understanding mechanisms underlying pituitary SSTR function will lead to the development of effective drug treatments for pituitary disorders.

Box 1 Challenges for assessing pituitary somatostatin receptor signaling

1. Human pituitary tumors are rare; malignant human pituitary tumors are exceedingly rare and fresh normal human pituitary tissue is generally unavailable.
2. Tissue availability is scarce. Pituitary tumors are small and usually resected in small fragments during transsphenoidal surgery; many tissue fragments are lost to operative suction.
3. Tumoral tissue is not devoid of blood vessels and areas of normal pituitary, especially during excision of micro-adenomas, which often contaminate small tumor samples.
4. Pituitary tissue SSTR expression is mostly assessed by qualitative or quantitative RT-PCR that also detects SSTR transcripts from associated normal tissue.
5. No human hormone-secreting pituitary cell line is available.
6. In vivo animal models for anterior pituitary tumors are limited, and do not robustly recapitulate human disease.
7. Pituitary cell cytoplasm is usually constrained; as a thin rim surrounds a large nucleus, visualization of receptor trafficking is challenging, especially for GH-secreting cells.
8. In vitro studies on SSTR over-expression in CHO, HEK-293, COS7 or other commonly utilized cell-lines might not accurately reflect signaling in the benign, slowly proliferating, highly-differentiated pituitary cell.
9. Highly sensitive and specific SSTR antibodies are not uniformly available. Immunostaining is often challenging unless the specific receptor is over-expressed.
10. As many pituitary cells express more than one SSTR, and expression might be inconsistent or regulated, it is difficult to distinguish between receptor-selective pathways upon SRIF stimulation.
11. As most SRIF ligands exhibit effective overlapping binding for more than one receptor subtype, it is difficult to distinguish between receptor-selective pathways upon SRIF stimulation.
12. SSTR neutral antagonists are not available for all SSTRs, and those available are not highly mono-receptor selective.

13. SSTR inverse agonists are not yet available to effectively study constitutive activity.
14. SRIF is a general inhibitory hormone which requires hormone induction to analyze ligand action on the cell. Most assays currently are not sufficiently sensitive to detect subtle changes in baseline hormone secretion *in vitro*.
15. Measurement of plasma SRIF levels is challenging due to sensitivity of the peptide to peptidase cleavage and therefore very short circulating half-life.

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Table 1

SRIF receptor subtype binding affinities.

Ligands		IC_{50} (nM)				
		hSSTR1	***hSSTR2***	***hSSTR3***	***hSSTR4***	***hSSTR5***
Endogenous	SRIF14 [a]	0.1–2.26	0.2–1.3	0.3–1.6	0.3–1.8	0.2–0.9
	SRIF28 [a]	0.1–2.2	0.2–4.1	0.3–6.1	0.3–7.9	0.05–0.4
	rCST14 [a]	1.7–5	0.09–1.8	0.3–3.8	0.2–18.2	0.3–1.9
	rCST29 [a]	2.8	7.1	0.2	3	13.7
	hCST17 [a]	0.25–7	0.6–0.9	0.4–0.6	0.5–0.6	0.3–0.4
Synthetic in clinical use or trial	BIM-23A760[b]	622	0.03	160	>1000	3.7
	Lanreotide [c]	180	0.5	14	230	17
	Octreotide [c]	575	0.4	38	>1000	9
	Pasireotide [c]	9.3	1	1.5	>100	0.16
Synthetic experimental	BIM-23120 [d]	>1000	0.3	412	>1000	190
	BIM-23206 [d]	>1000	128	>1000	>1000	2
	BIM-23268 [e]	18	15	62	16	0.4

[*] All tested in mono-receptor stable -K1, COS-7 or HEK-293 transfectants.

SRIF=somatostatin; r/hCTS=rat/human cortistatin

From:

[a] [129],

[b] Binding affinity to D2R is 15 nM[8],

[c] [130],

[d] [9],

[e] [10].

Table 2

Pituitary SRIF receptor subtype expression

		SRIF receptor subtype expression *					Detection method	Tissue studied	Reference
		SSTR1	SSTR2	SSTR3	SSTR4	SSTR5			
Fetal pituitary		+	+	+	+	+	A	human	[15]
Adult pituitary		+	+	+	−	+	A, D	Human, rat	[15,113,114]
Normal pituitary cells	GH	5	60	24	18	72	C, D	Rat	[115–117]
	ACTH	n/a	48	n/a	n/a	29	C, D	Rat	[115–117]
	PRL	n/a	18	n/a	n/a	46	C, D	Rat	[115–117]
	TSH	n/a	16	n/a	n/a	28	C, D	Rat	[115–117]
	FSH/LH	n/a	29	n/a	n/a	10	C, D	Rat	[115–117]
Pituitary tumor cell lines	AtT20[a]	−	+	+	−	+	B	mouse	[9]
	GH3[b]	+	+	+	+	+	A	rat	[30]
	TtT/GF[c]	n/a	+	+	−	n/a	B	mouse	[21]
	MMQ[d]	−	+	−	−	−	A	rat	[74]

* (+) or (−) indicates respective presence or absence of the specific SSTR in the cells indicated. Numbers indicate percentage of cells expressing the receptor.

A: reverse transcription PCR; B: quantitative reverse transcription PCR; C: In situ hybridization; D: Immunohistochemistry

[a] Cells from mouse pituitary tumor secreting ACTH;

[b] Cells from rat pituitary tumor secreting GH and PRL;

[c] Cells from mouse pituitary null (folliculostellate) tumor;

[d] Cells from rat pituitary tumor secreting PRL.

n/a = not available

Table 3

Human pituitary adenoma SRIF receptor subtype expression

	SRIF receptor subtype expression					Detection method	Number of tumors studied	Reference
	Positive tumors/total tumors tested (%)							
	SSTR1	**SSTR2**	**SSTR3**	**SSTR4**	**SSTR5**			
GH	21/36	87/100	23/47	2/40	84/104	A, B, C, D, E, F	111	[131–138]
	(53)	(87)	(51)	(5)	(81)			
ACTH	14/22	15/22	3/21	7/21	38/51	A, B, C, D	51	[93,135,136,139,140]
	(63)	(79)	(37)	(33)	(75)			
PRL	16/19	9/19	3/7	0/7	13/17	A, B, C, D	22	[107,136,137]
	(84)	(47)	(43)	(0)	(76)			
NFA	3/21	9/21	14/20	0/8	7/20	A, B, C, E, F	47	[133,135,136,141]
	(14)	(43)	(70)	(0)	(35)			
TSH	2/2	2/2	0/2	0/2	1/2	C	2	[137]
	(100)	(100)	(0)	(0)	(50)			

A: Solution hybridization; B: Ribonuclease protection assay; C: reverse transcription PCR; D: quantitative reverse transcription PCR; E: In situ hybridization; F: Immunohistochemistry. NFA = clinically non-functioning pituitary adenoma

Table 4

Factors regulating pituitary SRIF receptor expression*

Treatment	*SSTR1*	*SSTR2*	*SSTR3*	*SSTR4*	*SSTR5*	References
SRIF 14 (24–48 h)	up	down/up	up	up	up	[118,119]
Forskolin	up	up	n/a	n/a	none	[119,120]
GHRH	none/up	none/up	n/a	n/a	down	[119,121]
Ghrelin	none/down	none/down	n/a	n/a	down	[119,121]
17β estradiol	down/up	up	up	n/a	up/down	[108,122–125]
Testosterone	none/up	none/up	up	n/a	none	[125]
Thyroxine	up	n/a	n/a	n/a	up	[126]
Glucocorticoids (2 h)	up	up	none	n/a	n/a	[125]
Glucocorticoids (24–48 h)	down	down	down then up	n/a	none	[10,125,127]
Progesterone	up	none	down	n/a	n/a	[125]
Food deprivation	down	down	down	none	none	[118]
Diabetes mellitus	down	down	down	none	down	
TGFβ	n/a	up	n/a	n/a	n/a	[128]

* This table incorporates results from different species (pig, rat, and fish and humans), both genders, and assay techniques (in vitro and in vivo, primary cultures and cell-lines, mRNA transcript and promoter activation measurements); therefore an integrated interpretation of these observations might not all be extrapolated to human physiology. n/a = not available

Table 5

SRIF regulation of pituitary function

	Relevant pituitary cell process	SRIF effect	Pathways involved	Receptors involved
Pituitary hormones	Hormone synthesis	conflicting result	unknown	SSTR2
	Hormone packaging & trafficking	unknown	N/A	N/A
	Hormone degradation	unknown	N/A	N/A
	Hormone containing vesicle exocytosis	inhibition	Increased K^+, Decreased Ca^{2+}, Decreased cAMP	SSTR1, 2, 3, 5
Pituitary cell growth	Proliferation	inhibition	Increased PTP PI3K/Akt*	SSTR2, 5
	Apoptosis	stimulation	Increased PTP Inhibiting PI3K/Akt	SSTR2
	Senescence	unknown		

* Conflicting results whether PI3K/Akt is activated or inhibited.