Somatostatin system: molecular mechanisms regulating anterior pituitary hormones

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Abstract

The somatostatin (SRIF) system, which includes the SRIF ligand and receptors, regulates anterior pituitary gland function, mainly inhibiting hormone secretion and to some extent pituitary tumor cell growth. SRIF-14 via its cognate G-protein-coupled receptors (subtypes 1–5) activates multiple cellular signaling pathways including adenylate cyclase/cAMP, MAPK, ion channel-dependent pathways, and others. In addition, recent data have suggested SRIF-independent constitutive SRIF receptor activity responsible for GH and ACTH inhibition in vitro. This review summarizes current knowledge on ligand-dependent and independent SRIF receptor molecular and functional effects on hormone-secreting cells in the anterior pituitary gland.

Key Words
- somatostatin
- receptors
- pituitary
- hormone secretion

Introduction

The anterior pituitary gland is subjected to the stimulatory and inhibitory effects of multiple regulators. Somatostatin (SRIF) and its cognate receptors (sst1–sst5) exhibit a dominant inhibitory role in pituitary gland regulation. Hypothalamic SRIF was isolated from the hypothalamus (Burgus et al. 1973) and subsequently demonstrated to be secreted throughout the brain and from multiple peripheral organs, affecting multiple tissues (Patel 1999).

The pituitary gland is positioned outside the blood–brain barrier, and is composed of two entities that merge during embryonic development, the anterior and intermediate lobes that ascend from the oral ectoderm and the posterior lobe that descends from the hypothalamus (Drouin 2011). The anterior pituitary harbors hormone-secreting epithelial-origin cell types, including those expressing prolactin (PRL) and growth hormone (GH) that compose most of the gland, centrally located adrenocorticotropic hormone (ACTH)-secreting and thyrotropin (TSH)-secreting cells, and laterally scattered gonadotropin (follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) cells. The intermediate lobe contains cells secreting α-melanotropin; however, this lobe degenerates in humans. The posterior lobe harbors axons descending from neurons located in the hypothalamic nuclei and release vasopressin (antidiuretic hormone) and oxytocin (Bichet 2011). As various SRIF receptor expression levels and subtype profiles were observed on all pituitary cell types (Ben-Shlomo & Melmed 2010), a range of SRIF system effects are exhibited in the different cell types.

Cortistatin (CST), a ligand with SSTR binding affinity similar to that of SRIF, is expressed in the cerebral cortex and hippocampus, but not in the hypothalamus (Spier & de Lecea 2000); hence, it is not a major endocrine regulator of pituitary signaling and function.

SRIF receptors (SSTRs) exhibit in vitro constitutive activity, independently of SRIF or CST presence, and
regulate GH and ACTH production (Ben-Shlomo et al. 2009, 2013). The SRIF ligand and the five SRIF receptor subtypes (sst1–sst5) regulate pituitary function at two levels, via ligand exposure and potentially via selective receptors, independently of the ligand.

**Somatostatin**

Somatostatinergic neuronal cell bodies lie within the anterior periventricular nucleus and comprise 80% of hypothalamic SRIF immunoreactivity. The remaining hypothalamic SRIF-producing neuronal bodies lie within the paraventricular, arcuate, and ventromedial nuclei. Retrograde-tracing functional topography of hypothalamic SRIF neurons in the male rat demonstrated that SRIF neurons regulating the pituitary are confined within the periventricular and paraventricular nuclei, but not in the arcuate nucleus (Kawano & Daikoku 1988). These neurons send axonal projections to the median eminence at the base of the hypothalamus (Fig. 1). Ultrastructural morphometric analysis of SRIF-like immunoreactive neurons indicated that more than half of all terminals in the median eminence exhibit SRIF-containing vesicles with estimated 0.7 mM concentration per vesicle (Foster & Johansson 1985). Hypothalamic SRIF neuron axons descend from the median eminence toward the pituitary stalk and terminate at the pituitary portal blood vessel system, releasing SRIF into the blood reaching the anterior pituitary cells (Patel 1999) or travel through the neural pituitary stalk into the posterior pituitary (Patel & Srikant 1986; Fig. 2).

SRIF is cleaved from a common SRIF prohormone into several cyclic tetradecapeptide products by prohormone

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**Figure 1**

Somatostatin system: hypothalamus–anterior pituitary lobe axis. Somatostatinergic neuron bodies located at the hypothalamic periventricular (80%) and paraventricular (20%) nuclei travel through the median eminence and pituitary stalk and secrete SRIF into the pituitary portal circulation, reaching the cells of the anterior pituitary gland. Receptor subtype distribution is represented by subtype numbers (1–5) inside the specific cell type and is based on receptor profile in cell-respective human tumors, i.e. GH-, ACTH-, PRL, TSH-secreting adenomas and non-functioning pituitary tumors that also include gonadotroph FSH/LH secreting tumors. Large size red letter indicates that ~90% of selective tumor type are positive for that receptor subtype, medium size blue letter indicate that ~70% of selective tumor types are positive for that receptor subtype, small size black letters that ~50% of selective tumor type are positive for that receptor subtype. Lower percentages are not presented. Receptor profile data is based on Ben-Shlomo & Melmed (2010).
convertases (Galanopoulou et al. 1995); however, SRIF-14, which contains 14 amino acids, is the predominant form of SRIF in the brain, including the hypothalamus (Acunzo et al. 2008), and therefore the predominant pituitary regulator.

Multiple factors regulate hypothalamic SRIF-14 production and secretion. Table 1 lists factors demonstrated to have a direct effect on hypothalamic SRIF production and/or secretion. Of note, most studies utilized either ex vivo hypothalamic slices or hypothalamic primary cell cultures, attempting to isolate the effects of the studied molecule on SRIF.

SRIF half-life is short (~2 min) as it is rapidly internalized and inactivated by peptidases inside the cell after internalization (Roosterman et al. 2008) and in the circulation (Werle & Bernkop-Schnurch 2006). To overcome this limitation for clinical use, analogs such as octreotide (Bauer et al. 1982), lanreotide (Sassolas et al. 1989), and pasireotide (Bruns et al. 2002) were synthesized as stable SRIF agonists.

SRIF regulates pituitary function through the G-protein-coupled receptors (GPCRs): SRIF receptor subtype 1 (sst1), sst2, sst3, and sst5. The expression of sst4 in the normal adult pituitary gland remains unclear. Although sst2 is alternatively spliced to sst2a and sst2b, only the sst2a isoform is expressed in the human pituitary tumors (Panetta & Patel 1995). The five human SSTR genes are located on five different chromosomes and encode receptor protein of size ranging from 356 to 391 amino acid residues with 39–57% sequence identity among the receptors (homology derives mostly from the transmembranal domain; Patel 1999). Multiple factors that regulate SSTR expression levels (Ben-Shlomo & Melmed 2010) are provided in Table 2.

SRIF-14 exhibits high binding affinity (few hundreds pM in membrane extracts from cell transfectants in vitro) to all receptor subtypes (Patel 1999). Upon ligand binding, the receptors bind the Gα13 subunit of the Gα13/γ tetramer, releasing Gβγ, initiating multiple cascades of signaling pathways. Most studies on SRIF-14 regulation of pituitary

Figure 2
Selected SRIF-dependent pituitary signaling pathways. SRIF and SRIF analogs activate multiple molecular signaling pathways depicted here, which control pituitary hormone secretion as well as cell growth. These include Ca²⁺ and K⁺ channels, phosphatases such as SHP1 and PP2A, cyclic nucleotide synthases such as guanylyl and adenylyl cyclase, nitric oxide, NFκB, MAPK/ERK, PKC, as well as BMPs.
function have focused on sst2 and sst5; however, the adult pituitary gland expresses sst1 and sst3 that are yet to be explored in this context. Although SRIF signaling pathways in non-pituitary cells have been extensively investigated, with more than 20 such intracellular pathways described (Cervia & Bagnoli 2007), pituitary SRIF-mediated molecular signaling pathways has been mostly limited to ion channel regulation, adenylate cyclase/cAMP/PKA regulated pathways, and protein phosphatase activation (Ben-Shlomo & Melmed 2010).

### Table 1  Molecules regulating hypothalamic SRIF production

<table>
<thead>
<tr>
<th>Effect</th>
<th>Molecule</th>
<th>Method utilized*</th>
<th>References</th>
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<tbody>
<tr>
<td>Stimulation</td>
<td>Acetylcholine</td>
<td>Rat fetal hypothalamic primary cultures (d18)</td>
<td>Peterfreund &amp; Vale (1983)</td>
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<td></td>
<td>Dopamine</td>
<td>Male rat hypothalamic segments</td>
<td>Negro-Vilar et al. (1978), Maeda &amp; Frohman (1980) and Lengyel et al. (1985)</td>
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<td></td>
<td>Neurotransin</td>
<td>Rat hypothalamic segments</td>
<td>Sheppard et al. (1979), Maeda &amp; Frohman (1980) and Shimatsu et al. (1982)</td>
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<td>Melatonin</td>
<td>Rat hypothalamic segments</td>
<td>Richardson et al. (1981)</td>
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<td>Glucagon</td>
<td>Perfused hypothalamic halves of male rats</td>
<td>Shimatsu et al. (1982)</td>
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<td>Growth hormone</td>
<td>Rat hypothalamic segments</td>
<td>Sheppard et al. (1978)</td>
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<td>IGF1</td>
<td>Rat hypothalamic segments</td>
<td>Berelowitz et al. (1981)</td>
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<td></td>
<td>Sex steroidsb</td>
<td>In vivo and in vitro approaches. SRIF mRNA, protein, or hypothalamic neuron number</td>
<td>Werner et al. (1988), Zorrilla et al. (1990), Senaris et al. (1992), Simonian et al. (1998), Pillon et al. (2004) and Zhang et al. (2009)</td>
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<td></td>
<td>Thyroid hormones</td>
<td>Rat hypothalamic segments</td>
<td>Berelowitz et al. (1980)</td>
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<td>Cultured fetal rat hypothalamic cells</td>
<td>Berelowitz et al. (1982)</td>
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<td>Cultured fetal rat hypothalamic cells</td>
<td>Iwasaki et al. (1987) and Richardson et al. (1988)</td>
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<td>Insulin</td>
<td>Rat hypothalamic segments</td>
<td>Iwasaki et al. (1987)</td>
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<td>Cultured fetal rat hypothalamic cells</td>
<td>Iwasaki et al. (1987)</td>
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<td></td>
<td>Cultured fetal rat hypothalamic cells</td>
<td>Korbonits et al. (1999)</td>
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<td></td>
<td>GHRH</td>
<td>SRIF in the hypothalamic portal blood</td>
<td>Abe et al. (1981)</td>
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<td>CRH</td>
<td>Dispersed adult male rat hypothalamic cells</td>
<td>Negro-Vilor et al. (1978) and Richardson &amp; Twente (1990)</td>
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<td>TRH</td>
<td>Dispersed adult male rat hypothalamic cells</td>
<td>Sheppard et al. (1979)</td>
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<td></td>
<td>Bombesin</td>
<td>Dispersed adult male rat hypothalamic cells</td>
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<td>Norepinephrine</td>
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<td>Peterfreund &amp; Vale (1983)</td>
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<td>Substance P</td>
<td>Rat hypothalamic segments</td>
<td>Richardson et al. (1981) and Berelowitz et al. (1982)</td>
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<td></td>
<td>Cytokines: IL1 and IL2</td>
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<td>Quintela et al. (1997a)</td>
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<td>γ-aminobutyric acid (GABA)</td>
<td>Rat fetal hypothalamic primary cultures (d18)</td>
<td>Aguila (1998)</td>
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<td>Serotonin</td>
<td>Rat fetal hypothalamic primary cultures (d18)</td>
<td>Lengyel et al. (1985)</td>
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<td>Berelowitz et al. (1982)</td>
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<td>Quintela et al. (1997b)</td>
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<td>Acetylcholine</td>
<td>Male rat hypothalamic segments</td>
<td>Estupina et al. (1997)</td>
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<td></td>
<td>Vasoactive intestinal polypeptide (VIP)</td>
<td>Perfused hypothalamic halves of male rats</td>
<td>Estupina et al. (1997)</td>
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<td>Leptin</td>
<td>Fetal rat neurons in monolayer culture fragments</td>
<td>Quintela et al. (1997a)</td>
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<td>Somatostatin</td>
<td>Rat hypothalamic periventricular nucleus</td>
<td>Aguila (1998)</td>
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<td>Lengyel et al. (1985)</td>
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<td>Opioids</td>
<td>Rat hypothalamic fragments</td>
<td>Berelowitz et al. (1982)</td>
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<td>Glucose</td>
<td>Rat hypothalamic segments</td>
<td>Quintela et al. (1997b)</td>
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<tr>
<td></td>
<td>Cytokines: TGFβ</td>
<td>Primary monolayer cultures of hypothalamic cells</td>
<td>Estupina et al. (1997)</td>
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<td></td>
<td>Dual</td>
<td>In vivo injection induced while in vitro hypothalamic segment perfusion decreased SRIF secretion</td>
<td>Estupina et al. (1997)</td>
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*aAll experiments were carried out in male rats.

*bSome report decreased somatostatin level following sex steroid treatment (Fernandez et al. 1992, Hassan et al. 2001). This discrepancy may be due to the experimental approach including whether treatment was conducted in vivo or in vitro, treatment duration and dose, sex of the animal model and species.

SRIF-dependent pituitary molecular signaling pathways

SRIF-14 signaling in the anterior pituitary gland primarily mediates the regulation of hormone secretion, yet also plays a role in regulation of cell growth (Fig. 1).

### Ion channel regulation

The dominant function of SRIF-dependent pituitary signaling is the inhibition of stimulated hormone secretion.
Hypothalamic hormones (Bjoro et al. 1987, Spada et al. 1990, Bonnefont et al. 2000, Liu et al. 2006, Tsaneva-Atanasova et al. 2007) signal to release anterior pituitary hormone secretion by increasing intracellular Ca\(^{2+}\) levels, resulting in the exocytosis of hormone-containing vesicles. Most information related to SRIF-mediated ion channel regulation was accrued through the investigation of mechanisms for SRIF-dependent inhibition of GH secretion. Although the definitive role of individual ion channels in regulation of hormone secretion are not fully understood, advances have been made through the use of electrophysical methods in addition to molecular bio-chemistry, and physiological methods in addition to molecular biological approaches. Na\(^+\), Ca\(^{2+}\), and K\(^+\) channels have been isolated in somatotroph cell membranes and described to contribute to hormone secretion.

GH secretion is activated upon GH-releasing hormone (GHRH) binding and activation of somatotroph cell surface receptors. GHRH signaling causes membrane depolarization and an action potential burst in response to the opening of tetrodotoxin-insensitive Na\(^+\) channels. In turn, increased Ca\(^{2+}\) transient frequency and intracellular Ca\(^{2+}\) concentration lead to amplified exocytosis of GH-containing granules (Tsaneva-Atanasova et al. 2007). In contrast, SRIF antagonizes the effect of GHRH through membrane hyperpolarization by opening K\(^+\) channels leading to depletion of intracellular Ca\(^{2+}\) concentration, effectively inhibiting GH exocytosis (Kraicer & Spence 1981, Draznin et al. 1988, White et al. 1991, Tsaneva-Atanasova et al. 2007). SRIF signaling through sst2 and sst4 activates K\(^+\) influx through both inwardly rectifying channel conductance and delayed rectifying K\(^+\) channels in GH3 cells (Yang & Chen 2007). SRIF targets the large-conductance, calcium- and voltage-activated K\(^+\) channels (BK channel) in GH4C1 cells (White et al. 1993).

Ultimately, these effects result in membrane hyperpolarization and closure of L- and N-type voltage sensitive calcium channels (Petrucci et al. 2000, Cervia et al. 2002a, Tsaneva-Atanasova et al. 2007, Yang et al. 2007). SRIF-reduced T-type current occurs primarily in rat somatotroph cultures (Chen et al. 1990, Yang et al. 2007). In somatotroph cells, SRIF regulation of K\(^+\) currents are mediated by G\(_{\alpha}3\) (Chen 1997), while Ca\(^{2+}\) currents are mediated by G\(_{\alpha}2\) (Chen 1997, Degtiar et al. 1997), β1, β3 (Kleuss et al. 1992), and γ3 (Kleuss et al. 1993). In human GH-secreting tumor cultures, sst5-specific signaling is dependent on G\(_{\alpha}13\) (Peverelli et al. 2013).

SRIF-mediated inhibition of corticotropin-releasing hormone (CRH)-stimulated Ca\(^{2+}\) levels in human corticotropin-secreting pituitary adenomas is

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**Table 2** Factors regulating pituitary cell SRIF receptor expression. Table adapted and updated from Trends in Endocrinology & Metabolism, 21, A Ben-Shlomo & S Melmed, Pituitary somatostatin receptor signaling, 123–133, copyright (2010), with permission from Elsevier
Effectively blocked by pretreatment with pertussis toxin (PTX), indicating that the effect is Gαi/o dependent (Spada et al. 1990). SRIF-induced K⁺ influx is regulated by Gαi in AtT-20 corticotroph cells (Takano et al. 1997). Although it remains to be determined whether SRIF regulates pituitary Ca²⁺ levels independently of K⁺ channels, GH release correlates with both frequency and amplitude of calcium oscillations, while calcium channel blockers and SRIF acutely suppress Ca²⁺ extrusion (Holl et al. 1988). SRIF treatment resulted in Ca²⁺-dependent redistribution of cytoplasmic microfilaments, without affecting intracellular somatotroph GH content (Shimada et al. 1990), in addition to reduced association of exocytosis-associated RAB3B and SNARE proteins (Matsumoto et al. 2003).

Finally, it has been recently shown that SRIF inhibited CaMKIβ expression and protein levels, and knockdown of CaMKIβ decreases Ca²⁺ levels in GC cells and suppressed secretion, suggesting that CaMKIβ may mediate SRIF regulation of Ca²⁺ (Cervia 2011). In summary, although the role of SRIF-dependent regulation of ion channels in pituitary cell growth is unknown, SRIF-dependent regulation K⁺-derived membrane hyperpolarization and the reduction of Ca²⁺ influx and concentration mediate the acute regulation of the exocytosis of hormone-containing vesicles.

**Adenylate cyclase/cAMP/PKA signalling**

SRIF inhibits pituitary adenylate cyclase/cAMP/PKA signaling, thereby inhibiting pituitary hormone synthesis and cell growth. SRIF inhibits cAMP production and ACTH secretion induced by CRH, forskolin, isoproterenol, vasoactive intestinal polypeptide (VIP), and cholera toxin in AtT-20 cells (Heisler et al. 1982). Similarly, SRIF inhibits cAMP and GH production induced by GHRH stimulation in primary pituitary cells (Bilezikjian & Vale 1983). SRIF inhibits forskolin-induced cAMP/PKA signaling pathway in rat somatotropic cells (Tentler et al. 1997). sst1, sst2, sst3, and sst5 all mediate SRIF inhibition of adenylate cyclase in pituitary cells (Tentler et al. 1997, Cervia et al. 2003, Ben-Shlomo et al. 2005). SRIF inhibited forskolin-induced cAMP production, PKA activation, CREB phosphorylation, and transcription potency, while overexpression of the PKA catalytic subunit suppressed SRIF action in sst2 stable transfectant GH4 cells (Tentler et al. 1997).

The ability of SRIF to inhibit adenylate cyclase is Gαi/o dependent (Koch et al. 1985, Tallent & Reisine 1992, Liu et al. 1994, Morishita et al. 2003). In GH4C1 cells, SRIF-action is mediated specifically via Gαi2 (Liu et al. 1994), as PTX suppresses SRIF-mediated inhibition of VIP-induced cAMP (Koch et al. 1985). PTX treatment similarly attenuated SRIF action in GH4 cells overexpressing sst2 (Tentler et al. 1997). In addition, PTX attenuated SRIF-dependent inhibition of GHRH-induced GH in MtT/SGL somatotroph cells (Morishita et al. 2003). SST5-specific inhibition of forskolin-stimulated cAMP accumulation was dependent on Gαs in human GH-secreting tumor primary cultures (Peverelli et al. 2013). In AtT-20 cells, SRIF inhibition of adenylate cyclase and ACTH secretion is Gαs-dependent (Tallent & Reisine 1992). sst2, sst3, and sst5 mediate SRIF-dependent inhibition of cAMP in AtT-20 cells (Ben-Shlomo et al. 2005), as does sst1 in GC cells (Cervia et al. 2003). In chicken pituitary cells, SRIF inhibited GHRH-induced GH release by inhibiting cAMP/PKA signaling independent of calcium or protein kinase C (Donoghue & Scanes 1991). Although SRIF is classically an inhibitor of adenylate cyclase activity, there are reports using primary porcine somatotroph cultures in which both low and high doses of SRIF increased cAMP levels, suggesting a possible dual dose-dependent effect (Ramirez et al. 2002). As the mechanism by which this phenomenon occurs remains elusive, perhaps SSTRs, such as other GPCRs, might interact with not only Gαi/o proteins but also Gαs depending on the ligand context and receptor conformation. Therefore, SRIF-mediated inhibition of pituitary hormone secretion is both Ca²⁺ and cAMP dependent; as both Ca²⁺ concentration and cAMP levels are Gαs dependent, it is difficult to determine the relative contribution of each to hormone secretion and whether these mechanisms occur independently of each other.

**Protein phosphatase pathways**

SRIF-mediated regulation of pituitary protein phosphatase pathways is primarily associated with mechanisms controlling cell growth. SRIF is associated with increased protein phosphatase activity in both human GH-secreting pituitary adenoma cells and rat cell lines as well as human non-functioning pituitary tumors (Cervia & Bagnoli 2007). SRIF increases tyrosine phosphatase activity and was associated with the inhibition of cell growth in human GH-secreting pituitary tumor cells in vitro (Florio et al. 2003), while serine/threonine phosphatase activity participates in SRIF-mediated regulation of Ca²⁺ influx through dephosphorylation of Ca²⁺ and K⁺ voltage-activated (BK) channels (White et al. 1991). Octreotide exhibited antiproliferative effects in GH3 cells, mediated by both PTX-dependent and SHP1
(but not SHP2)-dependent mechanism (Theodoropoulou et al. 2006, Cerovac et al. 2010). Octreotide induced SHP1-dependent inhibition of the PI3K activity leading to the inhibition of PDK1 and Akt activity, ultimately leading to enhanced glycogen synthase kinase 3β (GSK3β) activity and upregulation of the tumor suppressor ZAC1 (ZACN; Theodoropoulou et al. 2006). Octreotide also increased the levels of rapamycin-suppressed phosphorylated insulin receptor substrate 1, subsequently decreasing phosphorylation of Akt through SHP1 (Cerovac et al. 2010). Interestingly, in acromegaly patients treated with octreotide, ZAC1 immunoreactivity correlated with insulin-like growth factor 1 (IGF1) normalization and tumor shrinkage (Theodoropoulou et al. 2009). Both octreotide and an sst2-specific agonist (BIM23120) induced apoptosis, and apoptosis-associated gene expression in human GH-secreting tumors is blocked by vanadate, indicating the involvement of protein phosphatases (Ferrante et al. 2006). Vanadate similarly inhibited SRIF and lanreotide-induced growth arrest in primary cultures of non-functioning pituitary adenomas (Florio et al. 1999). The role of SRIF-mediated regulation of protein phosphatase activity and growth arrest in non-pituitary cells has been described (Florio 2008). As, clinically, SRIF analog therapy induces pituitary tumor shrinkage, the mechanisms involved in SRIF-mediated protein phosphatase activation require further investigation. Moreover, the contribution of individual SSTR subtypes to phosphatase activation is still unclear.

Other SRIF-dependent pituitary pathways

Several other signaling pathways have been described to mediate SRIF action (Cervia & Bagnoli 2007, Otsuka et al. 2012), including MAPK, guanylyl cyclase, PKC, nitric oxide (NO), PI3K/Akt, and bone morphogenetic proteins (BMPs). The physiological relevance of these pathways to pituitary cell growth and hormone secretion remains unclear. Both octreotide and pasireotide decreased MAPK/ERK phosphorylation in both GH3 cells and in GH-secreting tumor cultures, and upregulated p27Kip expression (Hubina et al. 2006), while knockdown of sst5 increased ERK phosphorylation in AtT-20 cells (Ben-Shlomo et al. 2007). In human GH-secreting tumor cultures, sst5-dependent inhibition of ERK phosphorylation was dependent on Gzα5 (Peverelli et al. 2013). Octreotide activated PI3K/Akt and MAPK pathways through sst2 and sst5 in GH-secreting cells, inducing histone methyltransferases associated with menin, resulting in the upregulation of p27Kip and cell cycle arrest (Horiguchi et al. 2009). These discrepancies may suggest cell-type specificity or perhaps a similar dual role for SRIF action as that for adenylate cyclase regulation. SRIF was also shown to exhibit a dual dose-dependent effect on pituitary guanylyl cyclase regulation and cGMP accumulation (Vesely 1980).

SRIF inhibited both PKC-induced stimulation of GH secretion (Ikuyama et al. 1987) and NO-induced cGMP and GH levels (Bocca et al. 2000, Luque et al. 2005). SRIF blocked phospholipase A2-mediated GHRH- and thyrotropin-releasing hormone (TRH)-induced pituitary arachidonate release (Judd et al. 1986) and decreased arachidonate levels in GC cells (Cervia et al. 2002b). SRIF was also shown to induce apoptosis through NxFcB/JNK/caspase pathway (Ferrante et al. 2006, Guillermet-Guibert et al. 2007), and inhibited vascular endothelial growth factor production levels in pituitary tumor cells (Lohret et al. 2001, Zatelli et al. 2007). SRIF antagonized CRH-dependent inhibition of GSK3β activity in AtT-20 cells, inhibiting Wnt/β-catenin-mediated transcription and cell growth in a cAMP-dependent manner (Khattak et al. 2010). SRIF action in AtT-20 cells is dependent on BMP signaling. Inhibitory effects of octreotide and pasireotide on CRH-induced secretion in AtT-20 cells were attenuated by noggin, an inhibitory BMP-binding protein, suggesting that the endogenous BMP system is functionally linked to the mechanism of SRIF-mediated inhibition of secretion (Tsukamoto et al. 2010). SRIF-signaling in GH3 cells was similarly shown to be dependent on BMPs (Tsukamoto et al. 2011). Although it is evident that kinases and BMP growth factors are involved in pituitary SRIF signaling, our understanding of their regulation and functional consequences remain unclear.

Receptor phosphorylation, internalization, and desensitisation

Following activation of SSTRs by ligand, a feedback mechanism is activated leading to the receptor phosphorylation and internalization, ultimately initiating receptor desensitization and attenuated receptor-related signaling. As of yet, the only SSTR subtype described to follow this process in pituitary cells is sst2. sst2 was phosphorylated and internalized after treatment with SRIF and sst2-specific agonists in stable sst2 transfectant GH4C1 cells (Hipkin et al. 1997). sst2 is phosphorylated at five serine and threonine residues within the C-terminus following SRIF treatment (Liu et al. 2009). Moreover, in transiently transfected GH3 cells, both SRIF and octreotide, but not pasireotide, induced robust sst2 phosphorylation. Pasireotide stimulated selective residue
phosphorylation only upon GRK2 and GRK3 overexpression, yet resulted in only weak β-arrestin–sst2 complexes that easily dissociated (Poll et al. 2010). Prolonged SRIF stimulation leads to sst2 desensitization in both GH3 and AtT-20 cells (Hipkin et al. 1997), leading to attenuated responses to SRIF inhibition of cAMP production, and enhanced forskolin and CRH induction of adenylate cyclase and cAMP levels (Relisine & Axelrod 1983, Presky & Schonbrunn 1988, Ben-Shlomo et al. 2009).

While sst1 does not internalize (Sarret et al. 1999), there are conflicting reports regarding sst5 internalization. One study using transient sst5 transfectant GH3 cells found that the third intracellular loop of sst5 was involved in receptor phosphorylation and internalization following β-arrestin 2 binding (Peverelli et al. 2008). Yet, sst5 did not internalize following treatment with either SRIF or sst5-specific agonists in stable AtT-20 transfectants (Sarret et al. 1999, Ben-Shlomo et al. 2005). SRIF desensitization in stable receptor transfectant AtT-20 cells was dependent on sst2 and not sst5, as sst5 did not internalize in these cells (Ben-Shlomo et al. 2009). sst5 expression is unaffected by sst5 agonists or pasireotide in AtT-20 cells (van der Hoek et al. 2005, Ben-Shlomo et al. 2009), suggesting that sst5 remains biologically active in the membrane longer than sst2. In vitro studies may not accurately represent patterns of SRIF-dependent SSTR subtype-specific internalization and desensitization in vivo and therefore requires further study.

Any pituitary cell may express multiple sst receptor subtypes on the cell surface (Ben-Shlomo & Melmed 2010), suggesting that in addition to receptor subtype-specific signaling, receptor subtypes may form heterodimers, which may govern pituitary cell response to SRIF and SRIF analogs. Although sst receptor dimerization has yet to be demonstrated in pituitary cells lines, there is evidence of sst receptor hetero-dimerization when receptors are stably overexpressed in non-pituitary cell lines, and that dimerization does effect sst receptor function (Pfeiffer et al. 2002, Grant et al. 2008, War & Kumar 2012). While sst receptor subtypes are structurally and sequentially conserved throughout the body, it is likely that variation in receptor subtype expression contributes to the tissue specificity of SRIF-mediated molecular signaling, and should be further evaluated.

**SRIF-dependent pituitary hormone secretion**

SRIF exerts a primary effect on pituitary cells through acute inhibition of hormone secretion, specifically by suppressing exocytosis of hormone-containing vesicles. Although, it remains unclear whether SRIF-dependent inhibition of secretion is partially contingent on inhibition of cell growth arrest, as they usually occur concurrently following SRIF analog treatment of somatotroph tumors, there are reports of asynchronous hormone secretion and tumor shrinkage (Colao et al. 2009). In one such tumor, expression of sst5 was higher than sst2 levels, suggesting the potential of subtype-specific regulation of hormone secretion vs antiproliferative effects (Resmini et al. 2007).

Although SRIF is the primary inhibitor of pituitary GH secretion and is the main focus of this review, it should be noted that the neuropeptide CST, which shares structural homology to SRIF, has been reported to exhibit a similar inhibitory effect as SRIF on GH secretion both in vitro and in vivo (Broglio et al. 2002), yet the mechanism of action remains unclear as CST is reported to bind not only to SSTRs but also to the ghrelin receptor (GHS-R; Broglio et al. 2002). In contrast to the inhibitory role of CST on GH secretion, CST is reported to increase PRL release (Baranowska et al. 2009, Cordoba-Chacon et al. 2011). Unlike SRIF, CST has not been shown to be secreted from the hypothalamus directly into the pituitary portal system, and the exact role of CST in endocrine regulation of pituitary function in vivo is yet to be demonstrated.

**GH secretion**

The classical outcome of SRIF/sst signaling is the inhibition of hormone secretion, particularly that of GH from pituitary somatotroph cells (Giustina & Veldhuis 1998). Multiple factors and feedback loops regulate the release of SRIF from the hypothalamus and ultimately the control of GH secretion, including serum GH/IGF1 and glucose, as well as immobilization and exercise (Giustina & Veldhuis 1998). As SRIF inhibits GHRH-induced GH transcription and secretion by suppressing exocytosis of hormone-containing granules (Patel & Srikant 1986, Tentler et al. 1997, Morishita et al. 2003, Farhy & Veldhuis 2004), SRIF-null mice were expected to exhibit the characteristics of GH excess. However, despite moderately elevated GH levels, serum IGF1 levels were slightly elevated; however, body length and weight and IGF1 levels were unchanged (Low et al. 2001, Zeyda et al. 2001). Targeted hypothalamic delivery of lentiviral-shRNA against SRIF in young mice led to increased GH protein levels without effecting GH mRNA levels, yet serum levels of SRIF, GH, and IGF1, as well as body weight, were unchanged (Hao et al. 2010). These studies suggest that although SRIF may play an important function as an acute inhibitor of GHRH-induced...
GH secretion, it may have a less significant role in regulation of basal GH secretion.

While direct inhibition of pituitary hormone transcription has yet to be definitively associated with SRIF signaling, as some studies demonstrate a SRIF-dependent decrease in GH mRNA levels (Sugihara et al. 1993, Tsukamoto et al. 1994, Acunzo et al. 2008) others describe no change (Simard et al. 1986, Davis et al. 1989, Namba et al. 1989, Tanner et al. 1990, Gruszka et al. 2007), and some even demonstrate upregulation of gene expression possibly reflecting a GH-rebound effect after termination of SRIF treatment; the latter exemplifies the importance of outcome measurement timing. SRIF did not affect GH mRNA expression, but did suppress intracellular GH protein levels and decreased GH secretion in primary rat anterior pituitary cells (Simard et al. 1986). Similarly, SRIF inhibited GH secretion without affecting GH mRNA expression in primary human GH-secreting tumors cells (Davis et al. 1989). In cultured bovine pituitary cells, SRIF was able to suppress GHRH-induced GH expression, but had no effect on untreated cells (Tanner et al. 1990). Moreover, while sst2-specific and sst5-specific agonists suppressed GH secretion in human GH-secreting tumors, they did not affect GH transcription (Gruszka et al. 2012). Nevertheless, transient overexpression of sst2 in primary human GH secreting tumor cells modestly suppressed GH expression, in the absence of SRIF ligand (Acunzo et al. 2008).

Delineation of sst subtype-selective SRIF-mediated regulation of GH secretion remains unclear; however, both sst2 and sst5 and to a lesser extent sst1 play important roles in the inhibition of GH secretion. SRIF analog therapies targeting sst2 and/or sst5 for treatment of patients with GH-secreting pituitary tumors are effective at reducing serum GH and normalizing serum IGF1 levels (Melmed 2006). Moreover, treatment using compounds with affinity for sst2 and sst5 was 40% more effective at suppressing primary GH-secreting tumor GH secretion than sst2 or sst5-selective agonists individually (Shimon et al. 1997a). Increased sst2 membrane density in GH-secreting tumor cells enhances the sensitivity to sst2-selective agonists (Acunzo et al. 2008, Taboada et al. 2008). In normal fetal pituitary, both sst2 and sst5-specific agonists inhibit GHRH-induced GH secretion (Shimon et al. 1997b, Ren et al. 2003); however, co-treatment with sst2 and sst5-selective agonists was more effective than each individually (Ren et al. 2003). sst1-selective agonists similarly reduced GH secretion in both primary tumors cultures (Zatelli et al. 2003) as well as GC cells (Cervia et al. 2002a). Pasireotide, which binds all four receptor subtypes (sst5 > sst2 > sst3 > sst1), more effectively reduces serum GH levels in animal models compared with octreotide (sst2 > sst5 > sst3, but not sst1), and was recently demonstrated to have some advantage over octreotide in patients with acromegaly (Colao et al. 2014); however, the long-term efficacy of one drug over the other is yet to be proven (Petersenn et al. 2014a,b) and is still under current investigation.

Importantly, recent reports demonstrate a concentration-dependent, cell-specific effect of SRIF on GH-secreting cells, in both bovine and primates. While high-concentrations of SRIF inhibit GH-secretion, low-concentrations stimulate GH-secretion. sst1 and sst2 were shown to mediate the inhibitory effect of SRIF, while its stimulatory effect was signaled via sst5, all through adenylate cyclase–cAMP pathway and intracellular calcium level regulation. SRIF’s dose-dependent stimulatory/inhibitory effects should be further studied as they may have an important role in the physiological regulation of somatotroph cells (Luque et al. 2006a, Cordoba-Chacon et al. 2012).

Surprisingly, despite the dominant role of sst2 and sst5 in SRIF-mediated inhibition of GHRH-induced GH secretion, Sst2 and Sst5-null mice do not exhibit elevated serum GH levels (Zheng et al. 1997, Norman et al. 2002, Luque et al. 2006b). These results are, however, consistent with a potential, yet unproven, compensatory function of sst1 or sst3 regulating GH secretion in the absence of sst2 and sst5. Conditional knockout mice may provide a model to further elucidate the subtype-specific role of sst receptor subtypes in SRIF-dependent inhibition of GH secretion.

**PRL secretion**

SRIF-dependent control of PRL secretion is modest compared with that of GH. Treatment of prolactinoma samples with sst5-selective agonists effectively inhibited PRL secretion without affecting PRL expression (Shimon et al. 1997a, Jaquet et al. 1999, Fusco et al. 2008, Gruszka et al. 2012), while octreotide had no effect, likely due to the fact that sst5 is the predominantly expressed receptor subtype in human prolactinoma samples (Jaquet et al. 1999). Similarly, while octreotide exerted only modest effects, pasireotide strongly suppressed PRL secretion in prolactinoma tumor cultures (Hofland et al. 2004). PRL secretion was reduced upon SRIF treatment as well as an sst1-specific agonist in PRL-secreting pituitary tumors; the degree of PRL suppression correlated with sst1 expression levels (Zatelli et al. 2003). BMP4 enhanced the attenuating effect of pasireotide, but not of octreotide, on
forskolin-induced PRL in GH3 cells. Interestingly, BMP4 and BMP6 downregulated endogenous sst2 abundance, while increasing sst5 expression, and treatment with noggin rescued these effects. Moreover, noggin treatment increased octreotide sensitivity and decreased pasireotide sensitivity (Tsukamoto et al. 2011).

Several studies suggest that SRIF-dependent regulation of PRL secretion is estrogen-dependent. Female rats pre-treated with 17β-estradiol (E2) exhibited lanreotide-dependent reduction in lactotroph cell density and PRL secretion (Schussler et al. 1994). E2 treatment sensitized PRL-secreting tumor cells to SRIF and octreotide-dependent inhibition of PRL secretion, likely due to the upregulation of sst2 and sst3 (Visser-Wisselaar et al. 1997, Djordjijevic et al. 1998). Despite the inability of SRIF to inhibit PRL secretion in male rat primary lactotroph cultures, E2 treatment similarly sensitizes these cells to SRIF (Goth et al. 1996, Lee & Shin 1996). In addition, SRIF inhibits PRL induction by estrogen in male-to-female transsexuals, even more so upon co-treatment with cyproterone acetate, a compound with anti-androgen characteristics (Gooren et al. 1984). Taken together, the regulation of PRL secretion through SRIF-dependent pathways appears to be receptor subtype specific, BMP dependent, and sensitive to the presence of estrogen.

**ACTH secretion**

The role of SRIF signaling in the regulation of ACTH secretion from pituitary corticotroph cells remains unclear. SRIF did not affect basal or CRH (Stafford et al. 1989), ghrelin (Broglio et al. 2002), or angiotensin II (Volpi et al. 1996)-stimulated ACTH or cortisol levels in humans. Nevertheless, studies suggest that SRIF regulates ACTH secretion and is dependent on cortisol levels and cell milieu (Hofland 2008). Although SRIF did not affect basal or CRH-stimulated ACTH secretion in normal rat pituitary cells (Brown et al. 1984, Kraicer et al. 1985), SRIF inhibited CRH- and vasopressin-induced ACTH secretion in cultured pituitary cells derived from adrenalectomized rats and in serum starved cultures (Hofland 2008). Increasing cortisol levels in cell medium downregulated sst2 but not sst5 expression in corticotroph tumor cells that express both receptors (van der Hoek et al. 2007, van der Pas et al. 2013). Pituitary corticotroph cells were sensitized to octreotide in a serum-free environment, as well as after inhibition of the glucocorticoid receptor, which also downregulates sst2 expression (Lamberts et al. 1989a).

Ooctreotide and lanreotide, both clinically used as sst2 agonists, were ineffective in treating patients with Cushing’s disease (Hofland 2008), but were able to suppress ACTH levels in patients with hypercortisol-emia such as those with adrenal insufficiency (Fehm et al. 1976) and Nelson’s syndrome (Tyrrell et al. 1975, Lamberts et al. 1989b). However, pasireotide, which has preferential affinity for sst5, inhibits ACTH secretion in patients harboring ACTH-secreting adenoma despite hypercortisolism (Colao et al. 2012). The significance of SRIF-mediated signaling, particularly through sst5, has been further delineated through investigation of Srif-null and Sst5-null mice models; Srif-null mice exhibit elevated levels of Pomp mRNA expression (Luque et al. 2006b), and sst5-null mice have increased basal serum ACTH and cortisol levels (Strowski et al. 2003).

Importantly, downregulation of sst2 may not be the sole explanation to octreotide resistance as the drug was less effective than pasireotide at reducing ACTH secretion even after normalization of cortisol levels and rescued sst2 expression in preoperative Cushing’s patients (van der Pas et al. 2013). Therefore the contribution of other SSTRs expressed on corticotroph cells including sst3 and sst1 may play a role as well.

BMP signaling was shown to play a significant role in sst receptor-mediated inhibition of ACTH secretion in corticotroph cells. The BMP inhibitor noggin enhances CRH-induced ACTH secretion in AtT-20 cells and attenuated octreotide and pasireotide-mediated suppression of CRH-induced ACTH secretion. Octreotide and pasireotide increased BMP-Smad1/5/8 signaling and upregulated BMP type I and II receptors while simultaneously down-regulating inhibitory Smad6/7 (Tsukamoto et al. 2010). In summary, SRIF-mediated regulation of ACTH secretion appears to be sst receptor subtype specific and dependent on serum cortisol levels. The role of sst1, sst3, and BMP signaling pathways in the regulation of ACTH secretion require further investigation.

**Gonadotropin secretion**

Knowledge of SRIF regulation of human LH and FSH secretion is limited as pituitary tumors arising from gonadotroph lineages do not usually secrete FSH or LH and therefore do no result in a phenotype associated with hormone hypersecretion (Greenman & Stern 2009). Nevertheless, evidence suggests an inhibitory effect of SRIF on gonadotropin secretion. SRIF infusion suppressed gonadotropin-releasing hormone (GNRH)-induced LH and FSH in normal men (Millar et al. 1982) and inhibited LH pulse amplitude, but not frequency, without affecting FSH pulsatility (Samuels et al. 1992). SRIF does not affect
basal secretion of LH or FSH in cultured pituitaries from male rats (Yu et al. 1997), yet suppresses GnRH-induced LH but not FSH (Yu et al. 1997, Starcevic et al. 2002). In addition, SRIF suppressed gonadotropin levels in 60% of FSH-producing pituitary tumors and 30% of LH-secreting pituitary adenoma cultures (Klibanski et al. 1991).

TSH secretion

Although SRIF inhibits TSH secretion, the effect is less pronounced than that of GH secretion from somatotrophs (Patel & Srikant 1986). Both sst2 and sst5 were implicated in the suppression of TSH secretion (Shimon et al. 1997b); however, the relative contribution of individual receptor subtypes remains unknown. SRIF inhibited TRH-induced TSH secretion in normal adult males (Spoudeas et al. 1992). Similarly, SRIF suppressed TSH pulse amplitude and frequency (Samuels et al. 1992) and inhibited TSH levels in normal volunteers and in patients with primary hypothyroidism (Reichlin 1983). Octreotide and lanreotide reduced TSH secretion and normalized free thyroxine and free tri-iodothyronine levels in patients harboring pituitary TSH-secreting adenomas (Gancel et al. 1994, Beck-Pecoz & Persani 2002). Similarly, octreotide suppressed serum TSH concentrations in nine patients harboring TSH-secreting tumors, and similarly suppressed TSH secretion in cell cultures (Bertherat et al. 1992). TSH-secreting adenomas are extremely rare, limiting the ability to comprehensively study sst receptor subtype-specific regulation of TSH secretion.

In summary, SRIF is a dominant inhibitor of both basal and induced pituitary hormone secretion. There are clear indications that sst receptor-signaling pathway activation is receptor subtype- and density-specific, as well as cell type and context specific. While GH secretion is mediated predominantly through sst2, and to a lesser extent sst5, ACTH and PRL secretion appear to be coordinated for the most part through sst5 signaling. Further study is required to delineate SRIF receptor subtype specificity and to elucidate the role of sst1 and sst3 in pituitary hormone secretion.

SRIF-independent constitutive sst receptor activity

Constitutive receptor activity is the ability of a receptor to adopt an active conformation independently from its selective agonist (Seifert & Wenzel-Seifert 2002). Multiple GPCRs exhibit constitutive activity in their WT form and some by acquiring naturally occurring disease-causing mutations (Seifert & Wenzel-Seifert 2002).

Partial knockdown of sst2, sst3, or sst5 in mouse ACTH-secreting pituitary AtT-20 cells resulted in increased baseline intracellular cAMP levels and consequently ACTH secretion (Ben-Shlomo et al. 2007), while overexpression of either sst2 or sst5 in these cells resulted in reduced cellular response CRH via downregulation of CRH receptor subtype 1 (CRH-R1) expression (Ben-Shlomo et al. 2009). In addition, moderate sst2 overexpression in rat GH-secreting pituitary tumor cells (GC cell line) resulted in significantly decreased GH synthesis partially via GH promoter de-acetylation, which was not observed when a sst2 DRY-motif mutant lacking constitutive activity (Ben-Shlomo et al. 2013) was stably overexpressed. Inhibition of GH transcription was also observed when human pituitary cell primary cultures were infected with a low dose of sst2-containing adenovirus (Acunzo et al. 2008).

Utilizing a similar approach to study sst3 in GH-secreting cells, we show that stable sst3 transfectants exhibited suppressed basal intracellular cAMP levels, PKA activity, and inhibition of GH transcription, though to a lesser extent as compared with sst2 overexpression. sst3-mediated GH inhibition was not regulated epigenetically but rather via dephosphorylation and thus activation of GSK3β, a PKA substrate. The cells expressing non-constitutively active sst3 mutated at its DRY motif were unaffected (Eigler et al. 2014).

Constitutive sst receptor activity is yet to be proven in vivo. This is challenging as a naturally occurring, disease-causing, constitutively active SSTR mutant has not yet been characterized, and an SSTR inverse agonist is not available. Moreover, the SRIF system exhibits significant redundancy, as CST and SRIF bind all sst receptor subtypes with similar affinities and the receptors also share multiple signaling pathways. To rigorously study constitutive sst2 activity in vivo will require an animal experimental model that expresses neither ligands nor all other sst receptor subtypes, a difficult task.

Evidence in the literature suggests the possible presence of constitutive sst2 activity. Intriguing evidence from mice points to conditions in which SRIF (not sst2) is dispensable for determining baseline GH control. First, abolishing SRIF-producing rat hypothalamic neurons resulted in acutely increased serum GH levels, which normalized within 10 days, without altered pituitary GH-content (Soya & Suzuki 1990). Second, knockout Sifr (-/-), Cort (-/-), and double-knockout Sifr (-/-)/Cort (-/-) mice do not exhibit excessive growth.
(de Lecea and Castano 2006, Zeyda & Hochgeschwender 2008, Cordoba-Chacon et al. 2011). In addition, hyper-somatostatinemia elaborated by abdominal somatostatina tumors is not associated with GH deficiency (Oberg & Eriksson 2005, Galli et al. 2006). Observed negative association between sst2 and GH expression support the existence of a biological relationship between the two. For example, Srtf (−/−) mice exhibit 1.5- to threefold increase in GH levels along with 70% decrease in sst2 levels (Low et al. 2001, Zeyda et al. 2001). Glucocorticoids, acutely downregulate Sst2 promoter activity associated with increased pituitary GH synthesis in SRF-free conditions (Xu et al. 1995, Zeyda et al. 2001, Kajimura et al. 2003). In contrast, adrenalectomy (cortisol deficiency) increased rat somatotroph sst2 levels (Hofland et al. 2008). In addition, E2 lowers sst2 levels and increases baseline GH in the absence or presence of SRF (Cardenas et al. 2003, Borghi et al. 2006, Elango et al. 2006). Aromatase-null (i.e. E2 deficient) female mice exhibited high pituitary Sst2 gene expression with concomitant low GH levels, all reversed with E2 treatment (Yan et al. 2004). Importantly, female rats exhibit continuous GH secretion with higher baseline levels and also have lower Sst2 expression as compared with males, while male rats treated with E2 exhibited increased baseline GH and downregulation of sst receptors (Baumeister & Meyerhof 2000). In summary, when sst2 is decreased, GH is increased, with or without SRF. Although intriguing, the physiological importance of constitutive sst receptor activity is yet unclear in vivo. As absolute receptor number in the cell also determines observed constitutive activity level, receptor expression level regulation by SRF and other factors may control constitutive sst receptor activity.

Conclusion

SRIF system, i.e. hypothalamic SRF14 and its cognate sst1, sst2, sst3, and sst5 receptor subtypes, control pituitary gland function, mostly inhibiting anterior pituitary gland basal and induced hormone secretion. SRIF–sst receptor signaling pathway activation is receptor subtype specific and density specific, as well as cell type and context specific. SRF/sst2 is the main mediator of GH secretion while SRF/sst5 mainly mediates ACTH and PRL secretion. Sst receptor activation mediates its effect through multiple pathways, mainly adenylate cyclase/cAMP/PKA, MAPK, and ion channel regulation. SRIF-independent constitutive sst receptor activity is present in pituitary cells in vitro, inhibiting cellular cAMP and ACTH responses to CRH and GH transcription.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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