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Manuel D. Gahete, Mario Durán-Prado, Raúl M. Luque, Antonio J. Martínez-Fuentes, Rafael Vázquez-Martínez, et al.. Are somatostatin and cortistatin two siblings in regulating endocrine secretions? work ahead. *Molecular and Cellular Endocrinology*, 2008, 286 (1-2), pp.128. 10.1016/j.mce.2007.11.013 . hal-00531964

HAL Id: hal-00531964

<https://hal.science/hal-00531964>

Submitted on 4 Nov 2010

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Accepted Manuscript

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PII: S0303-7207(07)00431-5
DOI: doi:10.1016/j.mce.2007.11.013
Reference: MCE 6758

To appear in: *Molecular and Cellular Endocrinology*

Received date: 20-10-2007
Revised date: 17-11-2007
Accepted date: 17-11-2007

Please cite this article as: Gahete, M.D., Durán-Prado, M., Luque, R.M., Martínez-Fuentes, A.J., Vázquez-Martínez, R., Malagón, M.M., Castaño, J.P., Are somatostatin and cortistatin two siblings in regulating endocrine secretions? *In vitro* work ahead, *Molecular and Cellular Endocrinology* (2007), doi:10.1016/j.mce.2007.11.013

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**Are somatostatin and cortistatin two siblings in regulating
endocrine secretions? *In vitro* work ahead.**

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Short title: *in vitro* somatostatin and cortistatin actions

Keywords: cortistatin, somatostatin, sst receptors, pituitary, *in vitro*, endocrine, tumors, pancreas, thyroid

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Abstract

Somatostatin (SRIF) and cortistatin (CST) are two cyclic peptides sharing remarkable structural, pharmacological and functional similarities. Both peptides bind all somatostatin receptors subtypes (sst1-5) with comparable affinities, which may explain the considerable similitude between their actions, particularly on endocrine targets. However, the expression patterns of both peptides do not overlap in human tissues, and they are regulated by different stimuli, suggesting that SRIF and CST can exert unique roles. In fact, CST can bind other receptors, different to ssts (e.g. ghrelin receptor, GHS-R, and the MrgX2 receptor), which may be involved in those differential actions. In this review, we have summarized the limited knowledge gathered so far regarding the *in vitro* actions exerted by CST in different endocrine systems under normal and patho-physiological conditions, and have compared them with the well established functions known for SRIF on these systems. Available data suggests that CST substantially reproduces, but not fully mimics the "*in vitro*" effects of SRIF on pituitary secretions of human and animal models. Conversely, the functions of CST in the majority of peripheral endocrine (and non-endocrine) tissues are still unknown. Notwithstanding this, the differential tissue expression pattern of SRIF, CST and their receptors suggests that CST may act as a mere natural SRIF analogue in a number of tissues but in some endocrine tissues it may play a predominant, unique regulatory role with potential pathophysiological relevance. The challenge is now to find the genuine differences between these seemingly identical endocrine siblings.

Are SRIF and CST two endocrine siblings?

More than three decades ago, in the search of a growth hormone (GH) releasing factor, the group of Guillemin isolated and sequenced an ovine hypothalamic tetradecapeptide that displayed the opposite ability: it inhibited GH secretion. Accordingly, this hypothalamic peptide was named Somatotropin Release Inhibiting Factor (SRIF) or somatostatin (Brazeau et al., 1973). Since that time, it has been demonstrated that SRIF is more than a GH-inhibiting factor, which acts as a pleiotropic effector modulating multiple systems by acting on a broad range of tissues, including pancreas, intestinal tract, central nervous system, and immune cells (Patel, 1999; Moller et al., 2003; Olias et al., 2004).

More recently, use of molecular approaches led to the discovery of a new gene in several species including frog (Tostivint et al., 1996; Conlon et al., 1997), human and rodents (de Lecea et al., 1996), which was predicted to encode a protein related to SRIF. While the frog variant received the name of SRIF-II because of its similarity to SRIF, the elevated expression level of this gene in human cortex inspired its name, cortistatin (CST), in mammals. Further analysis has revealed that these two peptides share a remarkable sequential, structural and functional resemblance. For instance, SRIF and CST are synthesized as a pre-pro-peptide form that yields two different biologically active peptides, SRIF-14 and SRIF-28 in rat and human, and CST-17 (in human) or CST-14 (in rat) and CST-29 (in both species). In human, CST-17 and SRIF-14 share 11 amino acids, including the FWKT motif, which comprises the receptor binding core, as well as the two cysteine residues responsible for their conserved cyclic structure (for review see (Moller et al., 2003), de Lecea in this issue, and Tostivint et al., this issue).

This sequence identity and structural homology between SRIF and CST could explain their close pharmacology. Indeed, CST and SRIF exhibit a comparable

subnanomolar binding affinity to the family of receptors previously considered to be exclusive for SRIF, the ssts1-sst5, and both peptides possess the same ability to activate these receptors with similar efficiency and potency (Siebler et al., this issue), which could help to explain why both peptides share many actions at different targets (Moller et al., 2003) (Table 1). On the other hand, CST, unlike SRIF, has been reported to displace ghrelin from its binding sites in the human pituitary, which would likely correspond to the ghrelin receptor 1A (GHSR-1A) (Deghenghi et al., 2001), and also to bind to the Mrgx2 receptor (Robas et al., 2003), although this receptor seems to be somewhat promiscuous and more specific for proadrenomedullin and its related peptides (Nothacker et al., 2005). Nevertheless, it has been suggested that activation of these non-sst receptors by CST might be involved in the dissimilar or, in some instances, opposite actions that both peptides, CST and SRIF, play in the central nervous system or in immune cells (de Lecea and Castaño, 2006), Delgado et al., this issue. Indeed, whereas CST causes hypo-motility, depresses cortical excitability and increases slow wave sleep without affecting REM sleep, SRIF causes hyper-motility and enhances cortical excitability and REM sleep (de Lecea et al., 1996). Furthermore, CST (but not SRIF) has been reported to be a potential endogenous anti-inflammatory peptide, likely acting through a reduction in the production of inflammatory mediators by endotoxin-activated macrophages (Gonzalez-Rey et al., 2006).

The tissue expression patterns shown by SRIF and CST also suggest that these two peptides could play differential roles. In fact, *in silico* analysis of SRIF and CST mRNA distribution indicates that while SRIF expression is restricted to pancreas, brain, stomach, kidney, heart, connective and embryonic tissues, CST mRNA has a broader distribution, which overlaps with that of SRIF in those tissues, and also extends to other endocrine and non endocrine organs (Figure 1: obtained and adapted from

<http://www.ncbi.nlm.nih.gov/UniGene>). Moreover, it should be noted that although the expression patterns of SRIF and CST overlap in some tissues, this association does not necessarily imply their colocalization at cellular level. Thus, for example, whereas 50% of brain GABAergic neurons expressing CST also express SRIF, only 25% of neurons expressing SRIF also co-express CST mRNA (Spier and de Lecea, 2000). The possible presence of both peptides within the same cells in other tissues is still poorly explored, but solving this question will likely help to understand the differential roles exerted by each peptide in their diverse cell targets.

In spite of its broader distribution, which may also suggest a wider array of potential functions, the putative endocrine actions of CST have received hitherto little attention as compared to those investigated and reported earlier for SRIF (Table 1). This might be due, at least in part, to the fact that the majority of the *in vivo* and *in vitro* endocrine actions initially assayed for CST closely mimicked those previously reported for SRIF (Spier and de Lecea, 2000; de Lecea and Castaño, 2006; Broglio et al., 2007). However, it has to be emphasized that a thorough understanding of the pathophysiological meaning of this unique couple of related peptides and their family of common receptors will definitely require a careful comparative examination of their actions at different targets. In this scenario, it appears of interest to survey the data gathered to date on the regulatory actions exerted by CST on endocrine secretions both *in vivo* and *in vitro* and to analyze them in light of the corresponding available knowledge on SRIF. To this end, the *in vivo* endocrine actions of CST have been comprehensively reviewed in this same issue Broglio et al., 2007, and in the present review we have focused on the *in vitro* actions reported to be exerted by CST on endocrine cells as compared to those known to be effected by SRIF.

Actions of CST and SRIF on GH release from normal and tumoral pituitaries

There is a wealth of information regarding the actions of SRIF on somatotrope function, including the receptors and signaling mechanisms underlying inhibition of GH release (for review, see (Patel, 1999; Moller et al., 2003; Olias et al., 2004)). On the contrary, few studies have been conducted to examine the *in vitro* effects of CST on somatotrope function, perhaps because CST was initially regarded as a mere SRIF natural analogue with relatively low levels of expression in the hypothalamus (Spier and de Lecea, 2000). However, the study of the endocrine effects of CST has recently gained more interest, especially in that related to the control of pituitary hormone secretion, and, in particular, that involving GH synthesis and release.

In this regard, Rubinfeld *et al.* were the first to report that a 10 nM dose of CST-14 consistently inhibits basal GH secretion from human fetal pituitary cells in culture (Rubinfeld et al., 2006). Surprisingly, this inhibition was stronger than that exerted by equal doses of SRIF in the same cells (Rubinfeld et al., 2006). Conversely, in cultured porcine pituitary cells, CST not only inhibits GHRH-induced GH secretion as could be expected, but closely reproduces the dual, dose-dependent action of SRIF on GH release in these same pituitary cell cultures (Luque et al., 2006). Specifically, whereas high, submicromolar doses of CST abolished GHRH-stimulated GH release as previously reported for SRIF in this and other species, low, subnanomolar concentrations of CST directly stimulated GH release and did not alter the effect of GHRH (Luque et al., 2006), just as reported earlier for SRIF (Ramirez et al., 1997; Ramirez et al., 1998; Ramirez et al., 2002).

Intriguingly, results from the only report available hitherto on the response of rat pituitary cells in culture to CST indicate that whereas SRIF predictably inhibits basal GH release *in vitro*, CST-14 induces a direct, dose-dependent stimulatory effect on GH

secretion, reaching a maximum effect after 60 min of treatment (Baranowska et al., 2006). Further studies will be required to confirm this paradoxical action of CST in rats.

In contrast with the seemingly contradictory results reported in mammals, in cultures of frog pituitary cells both SS1, which corresponds to mammalian SRIF-14, and SS2, the counterpart of mammalian CST, dose-dependently inhibited GHRH-stimulated, although not basal, GH release (Jeandel et al., 1998).

The *in vitro* actions of CST on human pituitary somatotropic tumors, a classic target for treatment with somatostatin analogues, have also been explored recently. Specifically, the effect of CST on basal and GHRH-stimulated GH secretion was studied in human GH-secreting pituitary adenomas, including GH and mixed GH-PRL (Rubinfeld et al., 2006) where SRIF and its synthetic analogues have long been known to act as potent inhibitors (Moller et al., 2003). In particular, CST was found to effectively inhibit spontaneous GH release in six of the 13 (~50%) GH-secreting adenomas as well as in two of the three (~65%) mixed GH-PRL adenomas tested. Nevertheless, it should be noted that, depending of the pituitary adenoma tested, the efficacy of CST to inhibit GH release was variable when compared to that elicited in parallel by SRIF, octreotide and specific analogs for sst2 and sst5. In addition, CST also suppressed GHRH- and a ghrelin analog-stimulated GH release in cell cultures of one GH-secreting adenoma (Rubinfeld et al., 2006). Thus, although CST seems to act, by and large, as a natural SRIF analogue in regulating GH release from somatotropes, their actions are not always identical, thereby suggesting that a distinct set of receptor subtypes and/or molecular mechanisms can be differentially activated by these two peptides to finely tune the response of somatotropes under certain circumstances. Moreover, in view of the possible pathophysiological relevance of these differences, the study of those mechanisms deserves further attention.

Other SRIF actions on normal and tumoral pituitary cells

Although the somatotrope constitutes the primary cell target for SRIF in the pituitary, it has been reported that all the other endocrine cell types in this gland express somatostatin receptors and that their hormonal secretory activity can be sensitive to the inhibitory action of SRIF, although the particular type of sst involved and the sensitivity to SRIF varies largely depending on the cell type, species, and physiological situation considered (Patel, 1999; Moller et al., 2003).

Actions on lactotropes: SRIF has been shown to inhibit prolactin release *in vitro* from fetal human pituitary cells (Shimon et al., 1997), and, in earlier studies, from rat (Enjalbert et al., 1982) and fish pituitary cells (Grau et al., 1987). On the contrary, the potential inhibitory effect of CST on prolactin release under normal conditions has not been reported hitherto. Similarly, CST has been found to exert a suppressive effect on PRL secretion in most prolactinomas and somato-prolactinomas, being sst5 the main receptor involved in this inhibitory action (Rubinfeld et al., 2006).

Actions on corticotropes: SRIF has long been known to be able to negatively regulate ACTH secretion *in vitro* (Luque et al., 2006). In contrast, no data regarding the capacity of CST to regulate the secretion from corticotropes is available yet, despite recent pieces of evidence that point out the interest of comparatively analyzing the effects of both peptides. Specifically, several studies have recently helped to identify the major components involved in the response of corticotropes to SRIF, specially the receptor subtype sst5, and are also elucidating the mechanisms that may enable a pharmacological treatment of excess ACTH release from corticotropinoma cells causing Cushing's disease (e.g. using sst5-preferred analogues like SOM230, for review see Hofland et al, this issue and Schmid, this issue). Very recently, CST has been reported to display a similar strong

inhibitory effect than SRIF on the ACTH and cortisol hypersecretion in patients with Cushing's disease (Giordano et al., 2007), although the precise, central (CNS) and/or direct (pituitary) mechanisms employed by CST to exert these actions are not known yet, thereby emphasizing the interest in exploring the *in vitro* actions of CST on these cells.

Actions on gonadotropes: SRIF has rarely been found to modulate normal gonadotrope function *in vitro*. Thus, an isolated study on male rat anterior pituitary cells in culture showed that SRIF did not affect basal release of either LH or FSH, whereas it suppressed LHRH-induced release of LH, but not that of FSH (Yu et al., 1997). On the other hand, several studies have demonstrated that SRIF does inhibit gonadotropin release from human pituitary adenomas (both clinically nonfunctioning adenomas and somatotrope adenomas co-secreting the alpha-subunit). Specifically, SRIF suppressed gonadotropin secretion in 60% of FSH-producing tumors and 30% of LH-producing tumors, indicating that SRIF inhibits *in vitro* intact glycoprotein or free subunit secretion in the majority of both tumor types (Klibanski et al., 1991). Similarly, Saveanu *et al.* reported that SRIF analogues inhibited secretion of LH alpha-subunit in 33 % of cultured cells obtained from a macroadenoma (Saveanu et al., 2001). More recently, use of receptor-specific somatostatin analogs on clinically nonfunctioning pituitary adenoma cells cultured *in vitro* indicated that the regulation of alpha-subunit secretion by SRIF is mediated through the subtypes sst2A, sst3 and sst5 (Pawlikowski et al., 2007). Taken together, results from these and other reports suggest that although the overall efficacy of SRIF analogues on gonadotrope adenomas is only partial, its potential therapeutic use in this type of tumors deserves attention. In line with this, it is important to note that the direct actions of CST on gonadotropin secretion, either normal or in tumors, have not been reported hitherto, and that their study may shed light on this issue.

Actions on thyrotropes: SRIF has also been reported to inhibit stimulated thyrotropin release *in vitro* from fetal human pituitary cells (Shimon et al., 1997), as well as in cultures of pituitary cells from rats (Dieguez et al., 1984), birds (Geris et al., 2003) and amphibia (Table 1). In fact, in this latter species, it has been demonstrated that both SS1 (i.e. SRIF) and SS2 (i.e. the amphibian CST) inhibited TSH release induced by PACAP-38 but did not alter spontaneous (basal) TSH secretion, suggesting a similar role of both neurohormones in the regulation of thyrotrope function *in vitro* (Okada et al., 2006).

When viewed together, the data obtained in normal and tumoral pituitary cells in culture from mammals and non mammalian vertebrates suggest that the pleiotropic regulatory/modulatory capability of SRIF, and possibly of CST, on pituitary cell function could have evolutionary implications, and has definitely pathological and clinical significance. To date, the scarce effects tested for CST on pituitary cell function *in vitro* (except for somatotropes) reveal minimal differences with those previously observed for SRIF. Thus, it will be necessary to examine in detail those unexplored actions CST to ascertain whether there are unique functions for CST and SRIF in regulating pituitary cell function or whether these two peptides behave as identical, indistinguishable twins for this gland.

Extrapituitary actions of SRIF and CST on endocrine secretions.

In contrast to the abundant literature regarding SRIF actions in peripheral endocrine organs (for review, see Patel, 1999; Moller et al., 2003; Olias et al., 2004), there are still no reports on the *in vitro* actions of CST in other endocrine tissues distinct to pituitary (Table 1), despite the potential relevance of that information given that CST mRNA has a broader distribution than SRIF mRNA (Figure 1).

Pancreatic actions: CST is expressed in the endocrine pancreas (Papotti et al., 2003), where SRIF has long been known to play an important regulatory role. Indeed, pioneer studies showed for instance that SRIF acts as a potent inhibitor of both glucagon and insulin secretion acting directly on rat pancreatic alpha and beta cells (Efendic et al., 1974; Gerich et al., 1975; Brown et al., 1976). *In vivo*, it has been reported that CST displays the same inhibitory effects than SRIF on insulin secretion in either physiological and pathological conditions (such as patients with acromegaly or prolactinoma) (Grottoli et al., 2006, and Broglio's review in this issue). In recent years, a number of studies have used sst subtype selective agonists and antagonists to delineate the receptors and molecular mechanisms underlying the inhibitory actions of SRIF on insulin and glucagon secretion. Results from these studies, which are exhaustively reviewed by Strowski and Blake in this issue indicate that these multiple ssts would act in concert to convey the inhibitory signal of SRIF on insulin and glucagon release through an action that is species-dependent, and where it is critical the specific combination and the levels of expression of the ssts involved. Specifically, sst2 seems to be the main receptor mediating the inhibitory actions of SRIF in insulin and glucagon in humans, with sst1 and sst5 playing also a role in regulating insulin. In contrast, in rodents, sst5 appear as the predominant receptor mediating SRIF-induced inhibition of insulin release and sst2 seems to mediate glucagon inhibition (Strowski et al., 2000). In this scenario, and considering its local production in the islets, the study of the potential effects of CST on insulin and glucagon release will be of great interest.

Actions on thyroid gland: SRIF has also been reported to act on the thyroid, where it inhibits TSH-stimulated release of T4, and T3, as well as that of calcitonin from parafollicular cells (Patel, 1999). Furthermore, recent studies using the human medullary thyroid carcinoma (MTC) TT cell line have shown that the activation of specific ssts by its

selective ligands regulates diverse cellular processes, including proliferation, calcitonin secretion and RNA synthesis. Specifically, sst2 y sst5 seem to be the main receptors mediating the actions of SRIF on cell proliferation and calcitonin RNA synthesis while SRIF would act through sst1 to inhibit calcitonin release (Zatelli et al., 2002; Zatelli et al., 2002). However, to date no studies have been conducted testing the direct actions of CST on thyroid function.

Actions on other endocrine organs: SRIF has also been shown to be able to regulate *in vitro* endocrine secretions in other normal or tumoral peripheral organs like ovary and adrenal gland, which could be also potential pathophysiological targets for CST. In the ovary, SRIF acts as regulator of progesterone release. Specifically, SRIF was able to significantly inhibit the basal progesterone release from cultured human granulosa-luteal cells, but not that stimulated by LH (Holst et al., 1995). In the adrenal gland, it has recently been demonstrated that SRIF can also regulate secretion of catecholamines from chromaffin cells. In this case, SRIF does not inhibit but enhances the release of catecholamines induced by a high concentration of acetylcholine in bovine adrenal medullary cells (Ribeiro et al., 2006). However, to date no studies have been conducted testing the direct actions of CST on these organs.

There are a number of additional actions of SRIF related to the control of secretion, proliferation, etc in multiple tissues wherein CST might also play a role. As a relevant example given its therapeutic implications, it can be mentioned that SRIF can regulate ectopic secretions from pathological tissues. Indeed, SRIF regulated GHRH secretion from GHRH-secreting bronchial cancer cell cultures (Zatelli et al., 2005) thorough a mechanism that seems to differentially involve sst2, sst5, and sst1. However an exhaustive description of those additional targets would be out of the scope of this review.

Concluding remarks

As stated above, CST substantially reproduces, but not fully mimics the “*in vitro*” effects of SRIF on those pituitary secretions of human and animal models studied to date. This data would suggest a redundant role for both peptides in regulating endocrine targets. However, the function of CST in the majority of peripheral endocrine (and non-endocrine) tissues is still unknown. Moreover, the differential tissue expression pattern of SRIF and CST suggests that their functions are likely different rather than redundant in those tissues. The use of KO mice models may shed light on this issue. Thus, although earlier reports on SRIF KO female mice CST does not appear to be upregulated to “compensate” the lack of SRIF, a recent report indicates that loss of endogenous SRIF does up-regulate hypothalamic CST expression only in male mice (Luque and Kineman, 2007). These results suggest that CST actions could be gender-dependent in relation to the regulation of the hypothalamus-pituitary unit, a system wherein SRIF has already been shown to be highly dependent on sexual regulation. Accordingly, it would be of great importance to include this variable in the required detailed analysis that is still ahead to definitely establish the role of CST in regulating endocrine secretions. In this scenario, it can be envisioned that CST will act as a mere natural SRIF analogue in a number of tissues where the latter is to play the major role that is already well defined. However, in light of the available information on their distinct distribution, regulation and actions, it seems reasonable to propose that in some endocrine tissues CST may play a predominant, unique regulatory role over SRIF, with potential pathophysiological relevance. The challenge is now to find the genuine differences between these seemingly identical endocrine siblings.

Acknowledgements

This work was supported by CVI-139 and CTS-0175 (Plan Andaluz de Investigación, Junta de Andalucía, Spain), BFU2004-03883 and BFU2007-60180/BFI (Ministerio de Educación y Ciencia, Spain/FEDER) and CIBER Fisiopatología de la Obesidad y Nutrición CB06/03 (Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo) (to M.M.M. and J.P.C.).

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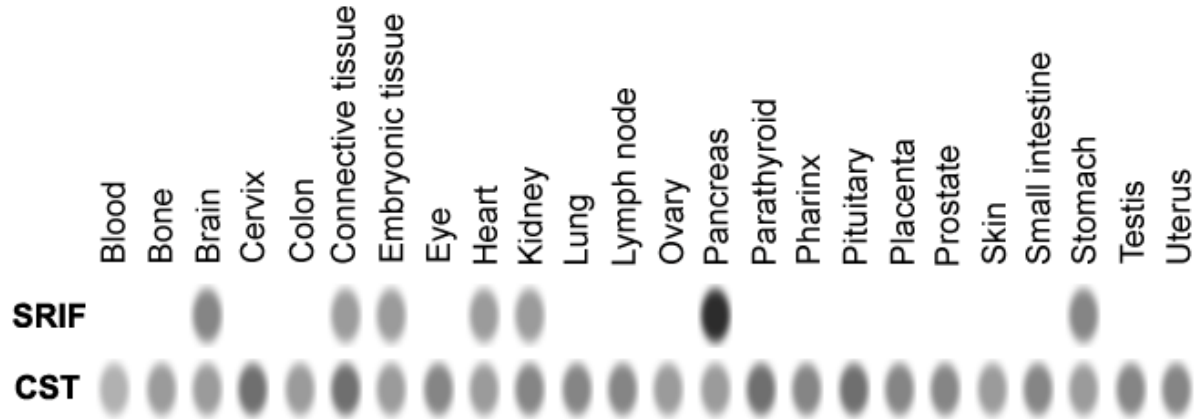


Figure 1: Tissue expression pattern of human SRIF and CST. The data is obtained and adapted from UniGene (<http://www.ncbi.nlm.nih.gov/UniGene>). Relative abundance of the transcripts in each tissue is indicated in different grey intensities where darker means higher expression.

TARGET		SPECIE	SRIF		CST	
			ACTION	REFERENCE	ACTION	REFERENCE
Pituitary	Normal	Rat	Inhibits GH secretion Inhibits LH but not FSH secretion	Brown, 1975 Yu, 1997	Stimulates GH release in a dose dependent manner	Baranowska, 2006
		Mouse	Inhibits CRH-induced ACTH secretion via sst2 and sst5	Strowski, 2002		
		Pig	Dose-dependent inhibitory and stimulatory effects on GH secretion	Ramirez, 1998 Ramirez, 2000	Dose-dependent inhibitory and stimulatory effects on GH secretion	Luque, 2006
	Adenoma	Chicken	Reduces sensitivity of thyrotropes to CRH. Does not affect basal GH or TSH secretion. Inhibits pituitary function through sst2 and sst5.	Geris, 2003		
		Bullfrog	Inhibits GRF-evoked stimulation of GH release	Jeandel, 1998	Inhibits GRF-evoked stimulation of GH release	Jeandel, 1998
		Human	Reduces PRL secretion, similar as sst1 analog but less than a sst5 analog Inhibits GH release via sst1, sst2 and sst5	Shimon, 1997 Zatelli, 2003 Shimon, 1997 Zatelli, 2003	Inhibits PRL release Inhibits basal GH secretion Suppresses GH response to GHRH	Rubinfeld, 2006 Rubinfeld, 2006
Pancreas	Rat	Down-regulates islets glucagon and insulin secretion	Efendic, 1974 Gerich, 1975, Brown, 1976			
	Mouse	sst2 inhibits glucagon secretion	Strowski, 2000			
Ovary	Normal	Human	Inhibits basal progesterone release. Does not inhibit LH-stimulated progesterone release	Holst, 1995		
Adrenal chromaffin cells	Normal	Bovine	Increases the release of catecholamines	Ribeiro, 2006		
Bronchial Carcinoid	Normal	Human	Inhibits ectopic GHRH secretion	Zatelli, 2005		

Table 1: Summary of the regulatory actions of SRIF and CST on endocrine secretions *in vitro*. The table presents some representative examples of the reported effects of these two peptides on endocrine tissues and compares their action where there is data available.