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Review

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

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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 pathophysiological 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.

Keywords: Cortistatin; Somatostatin; Sst receptors; Pituitary; *In vitro*; Endocrine

Contents

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1. 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 L., 2008; Tostivint et al., 2008).

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 sst1–sst5, and both peptides possess the same ability to activate these receptors with similar efficiency and potency (Siehler et al., 2008), 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; Gonzalez-Rey and Delgado, 2008). 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).

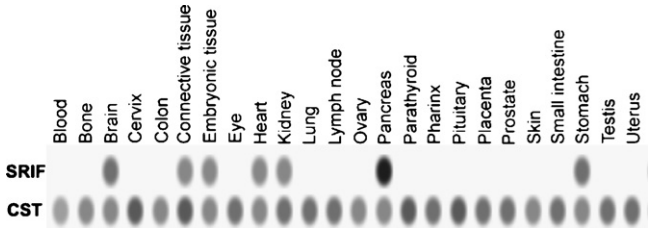

Fig. 1. Tissue expression pattern of human SRIF and CST. The data is obtained and adapted from UniGene (http://www.ncbi.nlm.nih.gov/UniGene). Relative abundance of the transcripts in each tissue is indicated in different grey intensities where darker means higher expression.

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 (Fig. 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., 2008), 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.