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Review

Somatostatin, cortistatin and their receptors in tumours

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Abstract

Somatostatin (SS) and its synthetic analogs have a role in the treatment of neuroendocrine tumours both in terms of symptoms control and antiproliferative activities. These effects are mediated by five SS receptors, widely expressed in both human neuroendocrine and non-neuroendocrine tumours, which were demonstrated to be diagnostically and therapeutically valuable targets. Cortistatin (CST), a brain cortex peptide, partially homologous to SS and having similar functions is also expressed in peripheral tissues and tumours. CST binds all SS receptors, and, differently from SS, also the ghrelin receptor GHSR1a and the CST specific receptor MrgX2. The expression profile of CST is mostly restricted to neuroendocrine tumours (gastrointestinal, pancreas, lung, parathyroid, thyroid, adrenal). In these tumours, CST probably acts via the SS or ghrelin receptor, the MrgX2 receptor being absent. Thus, in comparison to SS analogs, CST synthetic analogs may represent additional diagnostic/therapeutic tools in those tumours expressing the receptors for SS, for ghrelin or for both peptides.

Keywords: Somatostatin; Cortistatin; Somatostatin receptor; MrgX2 receptor; Human cancer; Neuroendocrine

Contents

1. Introduction

Somatostatin (SS) and cortistatin (CST) are two hormones sharing marked amino acidic sequence homology, as a result of a probable primordial gene duplication that finally lead to

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Table 1
SS and CST in human tumours: known ligand–receptor interactions

Ligands		Receptors
SS	⇒	sst 1-5
CST	⇒	MrgX-2
[Adreno-Medullin]	⇒	
[Ghrelin]	⇒	GHSR1a (GRN-R)

Abbreviations—SS: somatostatin; CST: cortistatin; sst: somatostatin receptors; GHSR: growth hormone secretagogue receptor; GRN-R: ghrelin receptor.

the occurrence of similar preprosomatostatin and preprocortistatin genes in chromosomes 3 and 1, respectively. Beside this duplication, other related genes may exist, including a mouse gastrointestinal peptide named thrittene, which has a 13/28 amino acid homology with somatostatin. SS and CST exert partially similar central and peripheral functions. Hypothalamic SS classically suppresses growth hormone (GH) and TSH release; insulin and other intestinal peptides are inhibited as well. Several other peripheral activities are known, for CST and SS, which act as neurotransmitters, neuromodulators, regulators of inflammation and immune function and finally, as regulators of (tumour) cell proliferation. Central activities of CST only partially overlap with those of SS, while CST and SS seem to share the same endocrine activities in humans (Bloom et al., 1974; Epelbaum, 1986; De Lecea et al., 1996; Gottero et al., 2004; De Lecea and Castano, 2006). The CST role in peripheral tissues and organs is less well understood, and only an effect on immune system and on tumour cell growth has been demonstrated so far (Cassoni et al., 2002; Dalm et al., 2004; De Lecea and Castano, 2006; Ferone et al., 2006).

The above-listed functions of SS and CST are mediated by a family of receptors that recognize these ligands with different affinity (see review in Patel, 1997, 1999). Originally, five different somatostatin receptor types (sst1-5) were identified and cloned and found able to bind not only native SS forms (SS-14 and SS-28), but also their synthetic analogs, such as octreotide, lanreotide and pasireotide (SOM230). Subsequently, CST was also shown able to bind all SS types, although not all emerging activities of CST could be explained by its binding to sst. In fact, other binding sites for CST were identified, including the ghrelin receptor on the one side (GHSR1a) and an apparent CST specific receptor on the other (MrgX-2). The latter was found capable of binding adrenomedullin as well (Kamohara et al., 2005). From this complex scenario (Table 1), it is evident that different hormones exert different functions, sharing or competing for different receptors in normal and altered central or peripheral tissues. While the role of SS in neoplastic conditions has been extensively studied, establishing the usefulness of SS analogs in the control of hormonal secretion and neoplastic growth in several neuroendocrine tumours, less clear remains the role of CST in the same tumours, as well as that of SS in non-endocrine tumours.

This review will highlight selected evidence of the expression of SS and CST family of ligands and receptors indifferent human tumour types, and of the antiproliferative effects of both their natural and synthetic analogs.

2. The ligands

2.1. Somatostatin expression in tumours

Somatostatin is an acidic polypeptide, which is widely distributed throughout the central nervous system,different peripheral tissues and organs. It is mainly produced by delta cells of the gastrointestinal tract and by pancreatic islets, but it is also present in the nervous plexuses of the intestinal wall. Tumours related to the aforementioned cells were shown to produce and secrete SS. SS-14 and SS-28 are the two biologically active forms of SS. Since the original description by Krulich et al. (1968) of a factor present in hypothalamic extracts able to inhibit GH secretion from the anterior pituitary cultured cells, several biological functions have been described for SS. These include a potent inhibition of basal and stimulated secretion from a wide variety of endocrine and exocrine cells, as well as neuromodulatory actions in the central nervous system, with effects on locomotory activity and cognitive functions (Epelbaum, 1986; Weir and Bonner-Weir, 1985; Bloom et al., 1974, 1975; Raynor et al., 1993a). SS also possesses antiproliferative properties and may be an important hormonal regulator of cell proliferation and differentiation (Lamberts et al., 1991).

Somatostatin-producing tumours (somatostatinomas) are rare functioning pancreatic neuroendocrine tumours (less than 2% of all abdominal endocrine tumours), having delta-cell morphology, high SS production and correlated clinical symptoms (so called “somatostatinoma syndrome”, characterized by steatorrhea, cholelithiasis, hyperglycemia and weight loss). Similar tumours occur also in the duodenum (Soga and Yakuwa, 1999; Hamy et al., 2001) and, more rarely, in the lung and paraganglia (DeLellis et al., 2004). These latter are generally unable to produce a clinical syndrome, despite immunoreactive SS being present in a cospicuous fraction of tumour cells (Dayal et al., 2004). A fraction of SS producing tumours is associated to familial syndromes including neurofibromatosis, von-Hipple-Lindau and multiple endocrine neoplasia type I (MEN1). Approximately half of cases are malignant and liver metastases are commonly observed (Moayedoddin et al., 2006). The above tumours have the organoid or trabecular histological structure typical of all neuroendocrine tumours and intensely express SS in the tumour cell cytoplasm. Other hormonal products, including cortistatin, can be co-expressed in a small percentage of tumour cells (Dayal et al., 2004; Low, 2004) (Fig. 1a and b).

Duodenal somatostatin-producing tumours generally contain characteristic psammoma bodies, composed of calcium crystals. Amyloid deposition is an additional possible feature of these tumours. Other human tumours may occasionally produce SS, including medullary thyroid carcinoma (Mato et al., 1998), endocrine pancreatic tumours with multihormonal activity (e.g. insulinomas or glucagonomas) (DeLellis et al., 2004), neuroblastoma and ganglioneuroma (Kogner et al., 1997),