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Activation of somatostatin 2 receptors in the brain and the periphery induces opposite changes in circulating ghrelin levels: functional implications

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Somatostatin is an important modulator of neurotransmission in the central nervous system and acts as a potent inhibitor of hormone and exocrine secretion and regulator of cell proliferation in the periphery. These pleiotropic actions occur through interaction with five G protein-coupled somatostatin receptor subtypes (sst1−5) that are widely expressed in the brain and peripheral organs. The characterization of somatostatin’s effects can be investigated by pharmacological or genetic approaches using newly developed selective sst agonists and antagonists and mice lacking specific sst subtypes. Recent evidence points toward a divergent action of somatostatin in the brain and in the periphery to regulate circulating levels of ghrelin, an orexigenic hormone produced by the endocrine X/A-like cells in the rat gastric mucosa. Somatostatin interacts with the sst2 in the brain to induce an increase in basal ghrelin plasma levels and counteracts the visceral stress-related decrease in circulating ghrelin. By contrast, stimulation of peripheral somatostatin-sst2 signaling results in the inhibition of basal ghrelin release and mediates the postoperative decrease in circulating ghrelin. The peripheral sst2-mediated reduction of plasma ghrelin is likely to involve a paracrine action of D cell-derived somatostatin acting on sst2 bearing X/A-like ghrelin cells in the gastric mucosa. The other member of the somatostatin family, named cortistatin, in addition to binding to sst1, also directly interacts with the ghrelin receptor and therefore may simultaneously modulate ghrelin release and actions at target sites bearing ghrelin receptors representing a link between the ghrelin and somatostatin systems.

Keywords: X/A-like cell, somatostatin receptor subtypes, ghrelin cell, somatostatin receptor agonists and antagonists, cortistatin

INTRODUCTION

In 1972, Guillemin’s group – while searching for additional releasing factors in hypothalamic extracts after their identification of thyrotropin-releasing hormone (TRH) – identified a novel negative regulator of pituitary somatotropic cells releasing growth hormone (GH; Brazeau et al., 1973). The cyclic peptide was named somatostatin (somatostatin release-inhibiting factor, SRIF), in keeping with its hypophysiotropic action (Guilleman, 2011). Somatostatin was found to be expressed in two biologically active isoforms: the tetradecapeptide somatostatin-14 (Brazeau et al., 1973) and the amino terminally extended octacosapeptide somatostatin-28 generated by differential post-translational processing from a common precursor molecule (Pradayrol et al., 1973). The cyclic pentadecapeptide somatostatin-14 (Brazeau et al., 1973) and the amino terminally extended octacosapeptide somatostatin-28 generated by differential post-translational processing from a common precursor molecule (Pradayrol et al., 1980). Thereafter, a flow of articles in rodents and humans established the ubiquitous distribution of somatostatin in various brain areas (Finsley et al., 1981; Johansson et al., 1984; Uhl et al., 1983) and peripheral organs including the gastrointestinal tract (Costa et al., 1977; Walsh, 1994). This was followed by the identification and characterization of five distinct, high-affinity, specific somatostatin receptors (sst) encoded by five distinct genes (Gahete et al., 2000a). Structurally, these receptors belong to the so-called “superfamily” of membrane G protein-coupled (GPC) receptors. The sst1−5 have distinct as well as overlapping patterns of distribution in the brain (Fehlmann et al., 2000; Spaey et al., 2008) and gut (Schafer and Meyerhof, 1999; Ludvigsen et al., 2004; Coletto et al., 2006) with a prominent expression of sst2 in the gastrointestinal tract (Sternini et al., 1997). Studies using new pharmacological tools, namely selective sst subtype agonists and antagonists (Grace et al., 2006; Cecato et al., 2010; Erchegyi et al., 2008, 2009, Table 1) point toward the role of different sst1−5 in mediating the large spectrum of somatostatin biological actions, mostly inhibitory in nature. Multiple effects of somatostatin can also result from the ability of sst to form both homodimers or heterodimers (sst, with sst1, or dopamine D1 receptor, sst2, with sst2, D1 or μ opioid receptor subtype 1) resulting in the activation of different intracellular signaling cascades (Rochelleville et al., 2000; Baragil et al., 2007; Schiller et al., 2008).

Of interest to neuroendocrinologists, somatostatin’s inhibitory action on pituitary GH release was soon extended to a wide range of hypothalamic hormones including prolactin, thyrotropin (thyroid-stimulating hormone, TSH), and adrenocorticotropic hormone (ACTH; Brown et al., 1984; Bertherat et al., 1995;
Table 1 | Structure and receptor binding affinity of somatostatin and somatostatin receptor agonists.

| Peptide | Structure | Peptide | Structure | Peptide | Structure | Peptide | Structure | Peptide | Structure |
|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|-----------|
| SST-14  | Ala-Gly-dCy5-Lys-Asn-Phe-3Phe-3Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH | SST-28  | Ser-Ala-Ala-Ala-Ala-Pro-Ala-Met-Ala-Pro-Arg-Glu-Ang-Lys-Ala-Gly-cCy5-Lys-Asn-Phe-3Phe-3Trp-Lys-Thr-Thr-Ser-Cys-OH | SST-41  | Thr-F(ab')2 | SST-42  | Thr-F(ab')2 | SST-80  | SST-125  |
| SST-28  | SST-14  |
| SST-41  | SST-42  |
| SST-80  | SST-125  |

Receptor affinities were derived from competitive radioligand displacement assays in cells stably expressing the cloned human receptor using 125I-labeled SST analogs. Values are expressed as IC50 (nM). SST-14: SST-28: SST-41: SST-42: SST-80: SST-125: SST-14: SST-28: SST-41: SST-42: SST-80: SST-125.

Shimon et al. (1987) as well as a large number of other studies have shown that the expression of somatostatin and its receptors is widespread throughout the brain and peripheral tissues. Somatostatin is expressed throughout the brain except in the olfactory bulb and the anterior hypothalamic nuclei. In the gastrointestinal tract, somatostatin is expressed in the endocrine cells of the gastric mucosa as the cognate ligand for the somatostatin receptor subtype 2 (sst2). Somatostatin is also expressed in the pancreas, where it is produced by the alpha cells, and in the Islets of Langerhans, where it regulates insulin and glucagon secretion.

In the past decade, a significant breakthrough came from the identification of ghrelin, a 28-amino-acid octanoylated peptide, which is predominantly produced by the endocrine cells of the stomach. Ghrelin stimulates food intake and gastric motility, and its plasma levels increase in the context of orexigenic and gastric prokinetic actions of the peptide. In addition, ghrelin signaling in the brain and the periphery exerts opposite influence on circulating ghrelin levels. The sst receptor subtype(s) involved in the regulation of ghrelin release by somatostatin will be of clinical relevance.

The present review focuses on recent evidence that somatostatin signaling in the brain and the periphery exerts opposite influence on circulating ghrelin levels. The sst receptor subtype(s) involved in the regulation of ghrelin release by somatostatin will be of clinical relevance.
BRAIN ACTIONS OF SOMATOSTATIN

The first function assigned to somatostatin was the inhibition of GH release (Brazeau et al., 1973). Now somatostatin is recognized to exert several central extrapituitary actions such as the regulation of other pituitary endocrine hormones especially those responsive to stress, parasympathetic and sympathetic outflow, thermogenesis, visceral functions, and behaviors. Namely, intracerebroventricular (icv) injection of somatostatin-28 inhibited the tail suspension stress-induced rise of circulating ACTH (Brown et al., 1984). This effect was mimicked by the stable pan-somatostatin agonist, ODTR-ST (Erchegyi et al., 2008) icv stimulated food intake in rats under basal as well as already stimulated conditions during the dark phase with a rapid onset (during the first hour) and a long duration of action (lasting for 4 h; Stengel et al., 2010a). ODTR-ST’s orexigenic action is sst2 mediated as it is reproduced by icv injection of the selective peptide sst2 agonist (Stengel et al., 2010d) and blocked by the selective peptide sst2 antagonist (Stengel et al., 2010a). This represents a central action since injected intraperitoneally at a 30-fold higher dose, the peptide did not influence food intake (Stengel et al., 2010d). The orexigenic effect of central sst2 stimulation observed in rats has been recently expanded to mice (Stengel et al., 2010c). A detailed analysis of the food intake microstructure using an automated food intake monitoring device showed that icv injection of the sst2 agonist increased the number of meals, shortened inter-meal intervals, and induced a higher rate of ingestion, whereas meal sizes were not altered (Stengel et al., 2010c). Collectively, these data indicate that brain activation of sst2 signaling pathways in rodents induces a rapid orexigenic response by decreasing satiety (number of meals), without influencing satiation indicated by normal meal sizes (Stengel et al., 2010c). The physiological role of brain sst2 signaling in modulating food intake is also supported by the decrease of nocturnal food intake induced by the peptide sst2 antagonist injected icv at the beginning of the dark phase (Stengel et al., 2010d). In addition, hypothalamic somatostatin shows a circadian rhythm with a peak in the early dark phase and a nadir in the early light phase (Card et al., 1999). Moreover, food restriction increases pituitary somatostatin release (Ishikawa et al., 2010) which could increase the drive to eat under these conditions.

PERIPHERAL ACTIONS OF SOMATOSTATIN

Contrasting to the central effects, somatostatin’s actions in the periphery are largely inhibitory. In the stomach, somatostatin delays emptying of the food (Smeltz et al., 1999) and inhibits

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gastric acid secretion which is mediated directly by an interaction with acid producing parietal cells but also via the reduced release of histamine from ECL cells and gastrin from G cells (Walsh, 1994). The acid-ant-secretory action of somatostatin is no longer observed in sst2 knockout mice, indicative of a primary role of the sst2 (Piqueras et al., 2003). Similarly, in the small intestine somatostatin reduces intestinal peristalsis in cats, rabbits and rats, while stimulating the duodenal, jejunal, and ileal contractile response in dogs (Tann et al., 1979). In line with the findings in rodents, somatostatin increases gastrointestinal transit time in humans (Gregersen et al., 2011). The effects on colonic motility are likely mediated by the sst1 and sst5 based on in vivo studies using circular and longitudinal human colonic smooth muscle cells (Corleto et al., 2006). In addition, somatostatin reduces visceral sensitivity with the sst5, playing a key role as indicated by visceral hypersensitivity to both mechanical and chemical stimulation in the jejunum of sst2 knockout mice (Bong et al., 2007). This finding is likely to be relevant in humans as well. Patients with irritable bowel syndrome injected subcutaneously with octreotide display an anti-hyperalgesic response as shown by the increased threshold of discomfort and pain using rectal barostat manometry compared to injection of placebo (Bradette et al., 1994; Schwaetz et al., 2004).

**Ghrelin and Its Receptor: Expression and Physiological Orexigenic and Prokinetic Actions**

**Expression and Regulation of Ghrelin and GHRELIN RECEPTOR**

Ghrelin bears a unique fatty acid (e-octanoyl) residue on the third amino acid which is essential for affinity and binding to the GRLN-R (Kojima et al., 1999; Kojima and Kangawa, 2005). Other dietary fatty acids of medium length can also serve as a direct source for the acylation of ghrelin (Nishi et al., 2005). The enzyme catalyzing the acylation of ghrelin was unknown for several years and just recently identified in mouse and human as a member of the membrane-bound O-acyltransferases (MBOATs), namely MBOAT4 which was subsequently renamed ghrelin-O-acyltransferase (GOAT; Gutierrez et al., 2008; Yang et al., 2008). GOAT mRNA and protein are prominently expressed in rodent and human gastric mucosa in ghrelin expressing cells (Sakata et al., 2009; Stengel et al., 2010b). In addition, GOAT protein has been detected in rodent and human intestine, pancreatic duct, gallbladder, hypothalamus and pituitary gland (Gahe et al., 2010b; Lim et al., 2011; Kang et al., 2012), rodent plasma (Stengel et al., 2010b) and human visceral and subcutaneous adipocytes (Rodriguez et al., 2012) leading to the speculation of additional acylation sites of ghrelin. Unlike ghrelin, desacetyl ghrelin, which does not bear the hydrophobic residue on the third amino acid, is the main circulating form. The acyl/desacetyl ghrelin ratio is 1:3 as recently reported using an optimized blood processing protocol to improve the yield of acylated ghrelin in rats (Stengel et al., 2009). Although desacetyl ghrelin does not bind to and activate the GRLN-R (Kojima et al., 1999), recent studies indicate that the peptide exerts several biological actions to influence food intake (Stengel et al., 2010b), reduce inflammatory somatic pain (Sibilia et al., 2012), muscle cachexia produced by injury in rats (Sheriff et al., 2012) and basal autophagy in human visceral adipocytes (Rodriguez et al., 2012). However, the understanding of the physiological function of this peptide is hampered by the fact that the desacetyl ghrelin receptor mediating its effects is still to be identified.

Blood levels of ghrelin vary in relation with the meal pattern with an increase before meals and a decrease thereafter (Cummins et al., 2001; Tschop et al., 2001a). In addition, fasting also increases ghrelin mRNA expression (Toshinai et al., 2001; Kim et al., 2003; Xu et al., 2009) and reduces ghrelin peptide content in the stomach (Toshinai et al., 2001; Kim et al., 2003) indicative of a stimulated production and release under conditions of food deprivation. Ghrelin levels are not only regulated by short-term variations in energy status associated with meal patterns but also by long-term changes in body weight. Ghrelin plasma levels are elevated under conditions of reduced body weight such as anorexia nervosa or tumor cachexia and reduced in obesity (Tschop et al., 2000, 2001b; Cummings et al., 2002). Similar to the ligand, the ghrelin acylating enzyme, GOAT is regulated by the metabolic status with an increased GOAT mRNA and protein expression in rodent gastric mucosa, hypothalamus, and pituitary following a 12- or 24-h fast (Gonzalez et al., 2008; Gahe et al., 2010b; Stengel et al., 2010b). Under conditions of obesity induced by high fat diet or leptin deficiency in ob/ob mice, a down-regulation of GOAT mRNA occurred in the mouse pituitary, unlike the stomach or hypothalamus (Gahe et al., 2010b), while patients with obesity-associated type 2 diabetes showed higher levels of GOAT in visceral adipose tissue (Rodriguez et al., 2012). This indicates a tissue specific regulation of GOAT under conditions of obesity.

**Orexigenic and Prokinetic Effects of Ghrelin**

Ghrelin is well established to stimulate food intake in line with its regulation by changes in energy status in many species including humans (Wren et al., 2000; Tzen, Christensen et al., 2004; Drue et al., 2005). It is so far the only known peripherally produced and centrally acting orexigenic peptide, contrasting with the numerous anorexigenic peptides in the gut (Surzaki et al., 2011). Ghrelin’s action is blocked by pharmacological or genetic approaches using GRLN-R antagonists (Salome et al., 2009) and GRLN-R knockout mice (Sun et al., 2004; Zigman et al., 2005) indicating a key role of ghrelin-GRLN-R interaction in mediating the orexigenic response. The food intake stimulatory action can result from ghrelin crossing the blood-brain barrier and binding to GRLN-R expressed on food intake regulatory brain nuclei (Banks et al., 2002; Pan et al., 2006) or acting directly on vagal afferents which also bear the ghrelin receptor (Date et al., 2002; Sakata et al., 2003). The respective role of these pathways under nutritional changes is still to be delineated. In addition to the stimulation of food intake, ghrelin is also involved in the regulation of body weight inducing an increase of body weight following chronic infusion of the peptide. This occurs through combined actions of stimulating appetite along with increasing fat storage and reducing lipid mobilization (Tschop et al., 2000; Strasburg et al., 2008; Davies et al., 2009). Further corroborating these findings, ghrelin and GRLN-R double knockout mice display an increased energy expenditure leading to a reduction of body weight (Pilger et al., 2008) which, however, could not be reproduced with a single genetic deletion of...
either ghrelin (Sun et al., 2003; Pfllger et al., 2008) or the GRLN-R (Pflüger et al., 2008). These differential phenotypes may reflect the functional relevance of the high constitutive activity of the GRLN-R (Darmian et al., 2012) and also give rise to the speculation that additional ligands for the receptor may exist (Deghenghi et al., 2001a).

DIFFERENTIAL MODULATION OF GH RELEASE BY GHRELIN AND SOMATOSTATIN

Ghrelin exerts endocrine actions opposite to somatostatin by stimulating anterior pituitary release of GH (Kojima et al., 1999; Yamazaki et al., 2002; Kojima and Kangawa, 2011), prolactin, and ACTH (Lanfranco et al., 2010). Somatostatin’s GH inhibitory effect is mediated by the sst1 (Briend et al., 1997), sst2 (Savaranu et al., 2001) and also sst3 (Krienenkamp et al., 1999). The GH releasing effect of ghrelin is blunted by intravenous (iv) infusion of somatostatin in healthy volunteers (Di Vito et al., 2002) and was completely blocked in pig pituitary cells in vitro (Malagon et al., 2003). The GH releasing action of ghrelin is likely to not only result from inhibiting somatostatin release (Feng et al., 2011) but also from direct activation of GH release (Wildhaus et al., 2006).

In addition, ghrelin and somatostatin antagonistically interact on hypothalamic arcuate cells to regulate the release of GHRH with an activation of these neurons following ghrelin and a reduction after application of somatostatin in vitro (Mori et al., 2000).

ACTIVATION OF BRAIN sst2 SIGNALING INCREASES BASAL AND PREVENTS VISCERAL STRESS-INDUCED SUPPRESSION OF CIRCULATING GHRELIN

Based on the established centrally sst2-mediated orexigenic action of somatostatin (Stengel et al., 2010a,b), we further investigated whether changes in circulating ghrelin may play a role. We found that the pan-somatostatin peptide, ODT8-SST (Table 1) injected ivc increased basal plasma acyl ghrelin levels in ad libitum fed rats (Stengel et al., 2005a). However, the rise was observed at 3 h postinjection and therefore unlikely to underlie the initial increase in food intake response to central ODT8-SST which occurred within the first hour. However, it may contribute to the sustained significant increase in cumulative food intake still maintained at 4 h after ivc injection of ODT8-SST (Stengel et al., 2010a). Other studies showed that activation of brain sst2 receptor prevents the decline in circulating ghrelin induced by visceral stress. Abdominal surgery reproducibly decreased the fasting plasma levels of acyl and desacyl ghrelin with a rapid onset and long lasting effect in rats (Stengel et al., 2010b, 2011b) resulting in lower circulating levels (Shi- mada et al., 2003; Silva et al., 2005; de la Cour et al., 2007). Such a response is in line with the inhibitory effects of somatostatin-sst2 on the endocrine secretion of other intestinal hormones (Pederson et al., 1975; Marco et al., 1983; Rokaus, 1984; Shizutani et al., 1991; Strowski et al., 2000). Likewise, in humans, peripherally injected somatostatin (Broglio et al., 2002; Norredlund et al., 2002) and somatostatin agonists such as octreotide (Barkan et al., 2003) reduce circulating ghrelin in healthy subjects. Of relevance, chronic subcutaneous infusion of the sst2/sst3/sst5 agonist octreotide-induced suppression of ghrelin plasma levels is not subject to rapid desensitization in rats and is likely to be sst2 mediated based on the prominent sst2 mRNA expression in
the rat stomach (Silva et al., 2005). Further support for a role of sst2 came from immunofluorescent double labeling studies detecting the protein expression of sst2 on ghrelin-producing X/A-like cells of the rat stomach (Stengel et al., 2011c) and similarly on human ghrelin-producing gastric mucosal P/D, cells (Fischer et al., 2008). Moreover, the selective peptide sst2 agonist, (Table 1) injected intravenously prevents the decline in circulating ghrelin induced by urethane (Stengel et al., 2011c). Convergent reports showed that abdominal surgery induces a rapid and sustained inhibition of circulating levels of ghrelin in rats (Stengel et al., 2010b, 2011b,c). Likewise, iv injection of the selective peptide sst2 agonist (Table 1) blocked the abdominal surgery-induced decrease of plasma ghrelin at 0.5 h postsurgery (Stengel et al., 2011c). The peptide is likely to act through paracrine transmission since somatostatin positive D cells directly contact ghrelin immunoreactive X/A-like cells in the rat stomach (Shimada et al., 2003). Interestingly, following abdominal surgery-induced decrease of plasma ghrelin at 0.5 h postsurgery (Stengel et al., 2011c). The peptide is likely to act through paracrine transmission since somatostatin positive D cells directly contact ghrelin immunoreactive X/A-like cells in the rat stomach (Shimada et al., 2003). Interestingly, following abdomi- nal surgery, acyl ghrelin was reduced more rapidly compared to desacyl ghrelin which was associated with a reduction of gastric as well as plasma concentrations of GOAT (Stengel et al., 2011c). Since blockade of peripheral sst signaling restores circulating levels of ghrelin (Stengel et al., 2011c), these data collectively suggest that peripheral somatostatin may blunt gastric GOAT mRNA expression and thereby negatively affect the acylation of ghrelin. In primary pituitary cell cultures somatostatin was reported to reduce GOAT mRNA expression and somatostatin knockout mice showed higher GOAT mRNA expression in the pituitary gland compared to their wild type (Gallet et al., 2010b). Based on these findings, somatostatin may influence ghrelin signaling not only via a direct inhibition of secretion but also by modulating the ghrelin activating enzyme GOAT. Further support for a physiological inhibitory action of peripheral somatostatin on ghrelin signal- ing came from somatostatin knockout mice that displayed an increased gastric ghrelin expression and higher circulating ghrelin levels compared to their wild type littermates (Laque et al., 2006a). These data indicate that endogenous somatostatin exerts a physiological inhibitory tone on gastric ghrelin synthesis and release.

During the past years, several clinical studies described ghrelin-producing NETs (Papotti et al., 2003; Dolm et al., 2004; Xidakis et al., 2003). Similarly to pro-somatostatin, cortistatin may possibly reside in the ability of cortistatin to bind and to activate the GRLN-R, whereas somatostatin does not (Deghenghi et al., 2001b; Muccioli et al., 2001). Divergent from native somatostatin, however, synthetic somatostatin ago- nists, lanreotide, octreotide, and vapreotide bind to the GRLN-R in human pituitary tissue (Deghenghi et al., 2001c) in addition to their selective affinity for sst2 > sst3 > sst5 (Bauer et al., 1982; Reichlin, 1983; Redding and Schally, 1984). In addition to binding studies, few functional findings also support the possibility that cortistatin may be another endogenous high-affinity ligand of the

**INTERACTION OF CORTISTATIN WITH GHR ELIN SIGNALING**

In 1996, the discovery of a new peptide sharing 11 of its 14 amino acids with somatostatin-14 was named cortistatin based on its predominant corticosteroidal and ability to depress cortical activity (de Lecea et al., 1996). Despite the chemical structure homology with somatostatin, both peptides are derived from distinct genes (de Lecea et al., 1997b). Similar to pro-somatostatin, processing of cortistatin precursor generated two mature products, cortistatin-14 and S29 in rodents and cortistatin-17 and S29 in humans (Fukusumi et al., 1997; Spier and de Lecea, 2000). Cortistatin is widely expressed in the brain, namely in the cortex and hippocampus, and although regional overlap exists, the distribution pattern differs from that of somatostatin (de Lecea et al., 1997b). Likewise, the peripheral expression pattern of cortistatin, (e.g., in adrenal, thyroid, and parathyroid gland, testis, pancreas, kidney, lung, liver, stomach, ileum, jejunum, colon, endothelial, and immune cells) does not fully match that of somatostatin (Papotti et al., 2003; Dolm et al., 2004; Xidakis et al., 2007). Consistent with being a close somatostatin endogenous analog, cortistatin contains the FWKT tetramer crucial for sst binding, and therefore displays high-affinity (1–2 nM) to all five sst subtypes where the peptide acts as an agonist (Fukusumi et al., 1997; Siehler et al., 2008). However, emerging evidence indicates that cortistatin induces distinct central and peripheral effects that differ from those exerted by the somatostatin-sst interaction such as central acetylcholine release, reduction of locomotor activity, depression of cortical activity, induction of slow wave sleep, anti-inflamatory and immune-modulatory effects, and reduction of vascular calcium deposition (for review, see Spier and de Lecea, 2000; Brogilio et al., 2007; Gonzalez-Rey and Delgado, 2008).

The existence of a specific cortistatin receptor has not been identified yet but differential actions between somatostatin and cortistatin may possibly reside in the ability of cortistatin to bind and to activate the GRLN-R, whereas somatostatin does not (Deghenghi et al., 2001b; Muccioli et al., 2001). Divergent from native somatostatin, however, synthetic somatostatin ago- nists, lanreotide, octreotide, and vapreotide bind to the GRLN-R in human pituitary tissue (Deghenghi et al., 2001c) in addition to their selective affinity for sst2 > sst3 > sst5 (Bauer et al., 1982; Reichlin, 1983; Redding and Schally, 1984). In addition to binding studies, few functional findings also support the possibility that cortistatin may be another endogenous high-affinity ligand of the somatostatin receptors.
GRLN-R. Cortistatin has been reported to inhibit vascular calcification induced experimentally in rats through activation of the GRLN-R receptor rather than sst or Mrg X2 (Liu et al., 2010). Of interest was the demonstration that cortistatin selectively upregulates the GRLN-R mRNA expression in cultured rat vascular smooth muscle cells, further indicative of an interaction between cortistatin and ghrelin signaling. Other studies in primates and mice demonstrated that endogenous cortistatin, unlike somatostatin, is involved in the stimulation of pituitary prolactin release, an effect that is blocked in vitro by the GRLN-R antagonist (Cordero-Chacon et al., 2011). However, most of the endocrine studies performed in vivo or in vitro showed parallel inhibitory responses between cortistatin and somatostatin consistent with the activation of classical somatostatin receptor subtypes (Broglio et al., 2008) with some exceptions (Prodam et al., 2008). This is further corroborated by the finding that cortistatin knockout mice display elevated circulating acyl ghrelin levels associated with an upregulated gastric ghrelin and G-AOX expression (Cordero-Chacon et al., 2011) indicating an inhibitory tone of endogenous cortistatin on ghrelin signaling.

To further delineate the actions of cortistatin mediated via the GRLN-R another peptide, cortistatin-8, has been shown to bind to the GRLN-R while being devoid of affinity to the sst subtypes (Laque et al., 2006b). However, in one clinical study cortistatin-8 did not influence spontaneous pituitary hormone secretion (GH, prolactin, and ACTH) and did not interfere with ghrelin’s endocrine responses when given in equimolar dose ratios in healthy human subjects (Prodam et al., 2008). Therefore, additional specific tools may be needed to characterize a possible direct link between the ghrelin and somatostatin signaling system via interaction on the GRLN-R.

**SUMMARY**

In summary, somatostatin robustly affects circulating levels of ghrelin through interaction with the sst. However, alterations vary with the site of action. Central somatostatin elevates plasma levels of acyl and desacyl ghrelin via interaction with brain sst2 and counteracts the visceral stress-related decrease in circulating ghrelin through pathways still to be elucidated in rodents. By contrast, the activation of peripheral somatostatin-sst1 inhibits circulating ghrelin levels in experimental and clinical studies and mediates the decline in circulating ghrelin induced by abdominal surgery in rodents likely via a paracrine action of somatostatin on sst1- bearing ghrelin cells in the stomach. Of interest, cortistatin, the other member of the somatostatin family, in addition to binds to and activates the GRLN-R. There is evidence that the peptide can exert a dual influence on ghrelin, by inhibiting its release through interaction with sst1 located on gastric ghrelin cells while activating GRLN-R at ghrelin’s tissue targets.

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