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The role of brain somatostatin receptor 2 in the regulation of feeding and drinking behavior

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Abstract

Somatostatin was discovered four decades ago as hypothalamic factor inhibiting growth hormone release. Subsequently, somatostatin was found to be widely distributed throughout the brain and to exert pleiotropic actions *via* interaction with five somatostatin receptors ($sst_{1\text{-}5}$) that are also widely expressed throughout the brain. Interestingly, in contrast to the predominantly inhibitory actions of peripheral somatostatin, the activation of brain sst_2 signaling by intracerebroventricular injection of stable somatostatin agonists potently stimulates food intake and independently, drinking behavior in rodents. The orexigenic response involves downstream orexin-1, neuropeptide Y_1 and μ receptor signaling while the dipsogenic effect is mediated through the activation of the brain angiotensin 1 receptor. Brain sst_2 activation is part of mechanisms underlying the stimulation of feeding and more prominently water intake in the dark phase and is able to counteract the anorexic response to visceral stressors.

Keywords

body weight; brain-gut axis; food intake; hypothalamus; satiation; satiety; somatostatin receptor; stress; water intake

Introduction

The 14 amino acid peptide, somatostatin was isolated in 1973 from 490,000 ovine hypothalami by Guillemin and colleagues as a potent inhibitor of growth hormone (GH) secretion from the pituitary *in vitro* and *in vivo* that led to its naming (Brazeau et al., 1973).

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Seven years later, Pradayrol et al. identified the N-terminally extended form, somatostatin-28, from porcine intestine (Pradayrol et al., 1980). In mammals, both somatostatin-14 and 28 originate from the prohormone, pro-somatostatin, which is generated after removal of a 24 amino acid signal sequence from the 116 amino acids precursor, pre-pro-somatostatin (Benoit et al., 1990). Somatostatin-14 and 28 bind with similar affinity to five distinct somatostatin receptor subtypes, sst_1 to sst_5 (Bruns et al., 1996; Patel, 1999). These receptors belong to the G-protein coupled seven transmembrane domain receptor family (Olias et al., 2004) and are related to the urotensin II receptors (Tostivint et al., 2014). In addition, spliced variants have been described for the sst_2 including the full length sst_{2a} and the C-terminally truncated form sst_{2b} in rodents (Cole and Schindler, 2000). Both, sst_{2a} and sst_{2b} splice variants bind somatostatin and display similar potency and desensitization rates (Cole and Schindler, 2000). In addition, several functionally active truncated forms of the sst_5 have been identified in humans and rodents (Cordoba-Chacon et al., 2010; Duran-Prado et al., 2009). These sst_5 splice variants display a differential subcellular localization (Cordoba-Chacon et al., 2010) and a reduced $[Ca^{2+}]i$ response compared to somatostatin (Duran-Prado et al., 2009).

Soon after the initially described inhibitory action of somatostatin on GH secretion, several extra-pituitary effects were identified in line with the widespread brain distribution of the peptide (Finley et al., 1981; Viollet et al., 2008). In rodents, somatostatin acts in the brain to increase body temperature and influence visceral functions (e.g. increase blood pressure through vasopressin-dependent mechanisms, decrease heart rate, prevent sympathetically mediated hyperglycemia and stimulate gastric acid secretion) (Brown and Taché, 1981;Brown, 1981; Brown, 1988; Hajdu et al., 2000). Somatostatin was also found to induce behavioral alterations of food consumption – either increase or decrease as discussed below – (Feifel and Vaccarino, 1994), increased grooming (Van Wimersma Greidanus et al., 1987) and locomotor activity (Vecsei and Widerlov, 1990). Other early studies also pointed to the central action of somatostatin-28 to counteract the activation of the hypothalamic pituitary adrenal (HPA axis) and sympathetic nervous system induced by acute stressors (Brown et al., 1984).

The review will focus on recent advances that unraveled mechanisms involved in the alterations of food intake induced by pharmacological activation of brain somatostatin signaling pathways. We will also address new evidence that somatostatin in the brain induces a potent dipsogenic response through distinct mechanisms independent from the stimulation of food intake. The role of endogenous brain somatostatin signaling will be reviewed in the context of its relevance in regulation of nocturnal feeding and drinking behavior in rodents and stress-related alterations of food intake (Sominsky and Spencer, 2014). Progress in the characterization of somatostatin receptors involved in these behavioral changes was greatly facilitated by the use of stable and selective peptide somatostatin agonists and the development of selective somatostatin receptor antagonists (Table 1) (Erchegyi et al., 2008).

Brain somatostatin signaling and the regulation of feeding behavior

Neuroanatomical support

Somatostatin (not distinguishing between 14 and 28) immunoreactivity was shown to be widely distributed in cell bodies and fibers of distinct nuclei throughout the rodent brain (Finley et al., 1981). In particular, dense somatostatin immunoreactivity is present in the hypothalamus, namely in the arcuate (Arc), ventromedial, periventricular and paraventricular (PVN) nuclei, and at the level of brainstem in the nucleus of the solitary tract (NTS) (Finley et al., 1981; Johansson et al., 1984; Moga and Gray, 1985; Viollet et al., 2008). These brain sites are well established to regulate food intake and energy balance (Schneeberger et al., 2014).

Consistent with the broad distribution of the ligand, the $sst_{1\text{-}5}$ are also widely expressed throughout the brain and – although overlap exists – the sst subtypes show a distinct expression pattern (Olias et al., 2004). With regards to feeding regulatory centers, a dense expression of sst receptors has been detected in the dorsomedial hypothalamic nucleus ($sst_1 = sst_3$), ventromedial hypothalamic nucleus ($sst_1 > sst_3 > sst_2$), PVN ($sst_{2a} = sst_3$) and Arc of the hypothalamus ($sst_1 = sst_{2a} = sst_3 > sst_4$), the NTS ($sst_1 = sst_2 > sst_3$) and the dorsal motor nucleus of the vagus nerve ($sst_{2a/b} = sst_4 > sst_5$) (Fehlmann et al., 2000; Hannon et al., 2002; Schindler et al., 1999; Schulz et al., 2000; Spary et al., 2008). Therefore, in feeding regulatory nuclei such as the Arc, PVN and NTS, both ligands and receptors are expressed. Interestingly, only the sst_2 and sst_3 are expressed in all three nuclei.

Orexigenic response to central injection of stable somatostatin agonists

Early on, studies reported that injection of somatostatin-14 or the stable $sst_{2,3,5}$ agonist octreotide (Table 1) into the brain stimulates food intake in rats (Table 2). Somatostatin or octreotide injected intracerebroventricularly (icv), into the dorsal hippocampus or anterior piriform cortex increased food intake in rats (Beranek et al., 1999; Danguir, 1988; Feifel and Vaccarino, 1990; Feifel et al., 1993; Rezek et al., 1976). More recent studies established that the stable pan-somatostatin agonist, ODT8-SST or octreotide injected icv at low doses (0.3 and 1 nmol/animal) induces a robust increase of food intake in *ad libitum* fed rats or mice under basal conditions during the light phase or already stimulated conditions during the dark photoperiod (when rodents usually eat) (Karasawa et al., 2014a; Karasawa et al., 2014b; Stengel et al., 2010a). The orexigenic response to icv injection of the stable somatostatin agonist, octreotide in rats is rapid in onset (within 10 min) (Beranek et al., 1999), reaches a peak response at the first hour post icv injection of the pan-somatostatin agonist, ODT8-SST and is long lasting (4 h) resulting in an enhanced cumulative food intake over a period of 9 h (Stengel et al., 2010a). A rapid orexigenic response to icv somatostatin (0.5 nmol) was also reported in non-mammalian species such as chicks under fasted or *ad libitum* feeding conditions (Tachibana et al., 2009).

However, at higher doses (1 – 3 nmol/rat, or 1 nmol/mouse, icv), somatostatin decreased food intake in rats and mice (Cummings et al., 1998; Feifel and Vaccarino, 1990; Lin et al., 1987; Nakahara et al., 2012; Vijayan and McCann, 1977) (Table 2). The anorexigenic effect at higher doses may be related to the confounding effects due to the occurrence of other

competing behavioral changes such as barrel rotation (Vecsei et al., 1989) and leakage into the peripheral circulation (Tannenbaum and Patel, 1986) – where the peptide largely exerts inhibitory effects (Bray, 1995). Taken together, activation of brain somatostatin signaling by icv injection of stable somatostatin agonists at low doses robustly increases food intake in rodents and non-mammalian species.

Role of brain somatostatin 2 receptor in the orexigenic effect

Further studies using selective sst receptor subtype agonists and antagonists (Table 1) delineated the primary involvement of the brain sst_2 receptor in the orexigenic response to icv injection of somatostatin agonists. This is supported by the demonstration that the sst_2 > sst_5 > sst_3 agonist, octreotide injected icv stimulates light phase food intake in *ad libitum* fed rats (Beranek et al., 1999; Danguir, 1988) and mice (Stengel et al., 2010b). This response is reproduced by the selective sst_2 agonist, S-346-011 injected icv (0.09 – 0.9 nmol/rat and 0.9 nmol/mouse, respectively), while the sst_1 (S-406-062) or sst_4 agonists (S-315-297, Table 1) injected at ∼0.25 or 0.8 nmol have no effect (Stengel et al., 2010b; Stengel et al., 2010c). Moreover, the action of the pan-somatostatin agonist, ODT8-SST was blocked by icv injection of the selective peptide sst_2 antagonist, S-406-028 (Table 1) in rats (Stengel et al., 2010a). Subsequent characterization of the sst_2-mediated meal pattern associated with the orexigenic response in mice showed that during the 0 – 4 h period post icv injection of the sst_2 agonist, S-346-011, there was an increase in the number of meals occurring after shorter intermeal intervals, whereas meal size was not altered compared to icv vehicle injected animals (Stengel et al., 2010b). These data indicate that the activation of sst_2 signaling in the brain suppresses “satiety” (mechanisms causing delayed onset of the next meal after one completed meal), while not influencing “satiation” (mechanisms causing meal termination) (Fekete et al., 2007).

Brain orexigenic circuits recruited by intracerebroventricularly injected somatostatin agonists

Pharmacological approaches indicate that several orexigenic signaling pathways, namely neuropeptide Y (NPY), opioid and orexin (OX) – through activation of Y1, μ and OX1 receptors, respectively – are involved in mediating the icv pan-somatostatin agonist, ODT8-SST-induced stimulation of food intake in rats (Karasawa et al., 2014b; Stengel et al., 2010a). Peripheral injection of the μ-opioid receptor antagonist, naloxone (Bodnar, 2004) completely prevented the orexigenic effect of icv injected pan-somatostatin agonist, ODT8-SST in rats (Stengel et al., 2010a). Likewise, in chicks the opioid μ-receptor antagonist, β-funaltrexamine injected icv prevented the stimulation of food intake in response to icv somatostatin, while δ or κ opioid antagonists had no effect (Tachibana et al., 2009). The opioid dependence and the demonstration that the sst_2 agonist, S-346-011 injected icv can further increase (1.4-times) already stimulated food intake induced by palatable high fat food in mice (Stengel et al., 2010b) suggest that sst_2 signaling may be involved in reward-induced eating (Gosnell and Levine, 2009). The interaction of sst and opioid signaling is further corroborated at the cellular level since the sst_2 has been shown to heterodimerize with the μ opioid receptor (Duran-Prado et al., 2008). However, whether this is linked with altered pharmacological and/or functional properties of sst_2 within brain reward centers needs to be investigated.

In addition to the μ receptor opioid antagonist, the Y_1 receptor antagonist, BIBP-3226 (O'Shea et al., 1997) or the OX_1 antagonist, SB-334867 (Smart et al., 2001) injected icv also completely blocked the orexigenic effect induced by icv injection of the pan-somatostatin agonist, ODT8-SST (Karasawa et al., 2014b; Stengel et al., 2010a). The demonstration that the sst_2 antagonist, S-406-028 did not alter the orexigenic response to icv orexin-A in rats indicates that the orexin-OX1 pathway is downstream to the sst_2 activation (Karasawa et al., 2014b). Other studies have established that the NPY-NPY1 signaling in the Arc is involved in the downstream mediation of orexin A's orexigenic effect (Yamanaka et al., 2000). Therefore, the signaling cascade targeted by icv injection of the stable pan-somatostatin agonist, ODT8-SST may involve the activation of the sst_2➔orexin-A-OX_1➔NPY-NPY_1 circuitry (Fig. 1). This assumption is supported by convergent neuroanatomical and electrophysiological studies showing that orexin-expressing neurons in the lateral hypothalamic area project to NPY-immunopositive neurons in the Arc (Horvath et al., 1999) and activate these neurons (Muroya et al., 2004; van den Top et al., 2004). Moreover, the food intake stimulation by icv orexin-A is blunted by icv injection of an NPY_1 antagonist (Jain et al., 2000). However, it cannot be ruled out that in addition, the pan-somatostatin agonist ODT8-SST acts by directly stimulating NPY signaling in the Arc as sst_2 receptors are localized on 50% of NPY expressing neurons in the Arc (Lanneau et al., 2000). The exact anatomical circuits by which somatostatin-sst_2 signaling stimulates OX_1 bearing neurons are still to be identified. Activation of sst_2 by icv injection of the pan-somatostatin agonist, ODT8-SST or a selective sst_2 agonist (S-346-011) induces Fos expression in the supraoptic nucleus and PVN, unlike in orexin-expressing neurons of the lateral hypothalamic area (Goebel et al., 2010) supporting an indirect action. GABAergic neurons are inhibited by somatostatin-sst_2 signaling in the brain (Chigr et al., 2001; Meyer et al., 1989) and may thereby reduce the inhibitory tone on orexin neurons, a hypothesis that warrants further investigation. Whether cannabinoid signaling is also involved in somatostatin's orexigenic effect as recently suggested based on the co-localization of CB1 and somatostatin in the PVN (Zou et al., 2015) will be subject to further studies.

Additional mechanisms modulating the somatostatin orexigenic response may involve the interplay with leptin, an adipose tissue-derived anorexigenic hormone that contributes to the long term regulation of body weight (Friedman, 1997). Somatostatin dampened leptin signaling as shown by the reduction in STAT3-phosphorylation level and nuclear STAT3 translocation in various hypothalamic nuclei, an effect mediated by several sst receptors (sst_3 > sst1 > sst_2) (Stepanyan et al., 2007). This could contribute to a reduction of leptin's anorexigenic action. Conversely, leptin injected icv reduced sst_2 protein expression in the rat hippocampus (Perianes-Cachero et al., 2012) followed by a delayed increase of sst_2 protein expression (Perianes-Cachero et al., 2013) which may be a counter-regulatory mechanism to balance leptin's action in the rat brain. In an *in vitro* preparation of rat fetal hypothalamic neurons, leptin also decreases somatostatin mRNA expression and somatostatin secretion under basal as well as NPY stimulated conditions (Quintela et al., 1997) further underlining the antagonistic interplay between these two hormones. Taken together, somatostatin's action in the brain is likely to be exerted *via* sst_2 signaling stimulating orexigenic pathways: sst_2➔orexin-A-OX_1➔NPY-NPY_1 and may also involve inhibiting the leptin anorexigenic pathway (Fig. 1).

Central action of somatostatin on energy metabolism

The robust increase in food intake observed after acute icv injection of the pan-somatostatin agonist, ODT8-SST (1 nmol/rat) in rats was accompanied by an increase in energy expenditure as assessed by indirect calorimetry (Stengel et al., 2010a). The peptide also increases body temperature and grooming under these conditions (Stengel et al., 2010a). These functional alterations may – at least in part – contribute to the observed decrease in body weight at 24 h after the icv injection (Stengel et al., 2010a).

Dipsogenic response to central injection of somatostatin agonists

Two earlier studies reported that the icv injection of low doses of the stable somatostatin agonist, octreotide (0.01 – 0.4 nmol) increased water consumption when assessed without food for a 10-min period post injection (Hajdu et al., 2000; Hajdu et al., 2003). In the presence of food, the somatostatin peptide agonist stimulates first drinking behavior within 1 min followed by eating after 10 min (Beranek et al., 1999). These reports were the first observations indicative of a dipsogenic effect, independent of food intake, induced by injection of the somatostatin agonist. Recent studies demonstrated that the activation of brain sst receptors by icv injection of endogenous ligands, somatostatin-14 or cortistatin, a structurally related peptide (de Lecea, 2008) which activates sst_1-sst_5 with binding affinities comparable to those of somatostatin-14 (Siehler et al., 2008) or the pan-somatostatin agonist, ODT8-SST (0.6 nmol/rat), stimulates water consumption in rats deprived of food (Karasawa et al., 2014a). The dipsogenic response was observed only during the first 10 min after icv injection of somatostatin or cortistatin and maintained for 60 min after icv injection of ODT8-SST (Karasawa et al., 2014a).

Interestingly, when food intake was assessed without water or water intake without food for 1-h, the pan-somatostatin agonist, ODT8-SST stimulated both food and water intake, while somatostatin-14 and cortistatin rapidly (within 10 min) stimulated water but not food intake in rats (Karasawa et al., 2014a). This may be related to the short half-life of somatostatin-14 and cortistatin compared to the stable pan-agonist, ODT8-SST not allowing these endogenous peptides to reach feeding-regulatory centers, while those regulating thirst are affected (Karasawa et al., 2014a). The demonstration that in rats with access only to either food or water or both concomitantly, icv ODT8-SST induces a dipsogenic response of similar magnitude, further supports the independence of water intake from that of food consumption (Karasawa et al., 2014a).

Role of somatostatin 2 receptor

Convergent pharmacological evidence established that the dipsogenic response to icv injection of the pan-somatostatin agonist, ODT8-SST and cortistatin in rats is primarily mediated by the sst_2 receptor. Reports showed that the selective sst_2 agonist (S-346-011, 0.8 nmol, icv) stimulates water intake with a similar magnitude to that of icv ODT8-SST or cortistatin in rats deprived of food during the test (Karasawa et al., 2014a). By contrast, the sst_1 agonist (S-406-062) or sst_4 agonist (S-315-297, Table 1) under the same conditions had no significant effect (Karasawa et al., 2014a). Moreover, icv injection of the sst_2 antagonist

(S-406-028) completely prevented the dipsogenic response to icv ODT8-SST and cortistatin (Karasawa et al., 2014a).

Mechanism of action

The activation of the brain sst_2 receptor-induced dipsogenic response involves downstream angiotensin II-angiotensin-1 (AT_1) receptors well established to regulate thirst and fluid maintenance (Fitzsimons, 1998). Saralasin, an AT_1 and AT_2 receptor antagonist or the AT_1 antagonist, losartan injected icv in rats without access to food completely blocked the stimulation of water intake induced by icv injection of the stable somatostatin agonists, octreotide and ODT8-SST or cortistatin (Hajdu et al., 2000; Karasawa et al., 2014a). Moreover, icv octreotide induced the release of angiotensin I in the rat hypothalamus within 10 min (Gardi et al., 2001). By contrast, the angiotensin II-induced increase of water consumption in rats was not altered by a selective sst_2 antagonist further supporting the action of angiotensin II signaling downstream of the somatostatin-sst_2 receptor pathway (Karasawa et al., 2014a).

Although the exact neuroanatomical substrate(s) through which sst_2 receptor activation recruits the brain angiotensin-AT_1 system (McKinley et al., 2003) remains to be determined, indirect evidence supports the PVN as a site of action. The pan-somatostatin agonist, ODT8-SST or the sst_2 agonist injected icv did not activate the subfornical organ (SFO) or median preoptic nucleus while activating magnocellular neurons in the PVN and supraoptic nucleus (Goebel et al., 2010; Karasawa et al., 2014a). These hypothalamic nuclei are part of the angiotensinergic system descending from the SFO and organum vasculosum's lamina terminalis (Fitzsimons, 1998; Miselis, 1981). Other evidence shows that icv injection of angiotensin II induces c-Fos/c-Jun prominently in neurons of the PVN and SON co-expressing the AT_1 receptor (Moellenhoff et al., 2001). Moreover, the PVN and surrounding areas are sites of action for the somatostatin agonist, octreotide to induce a drinking response in rats (Hajdu et al., 2003). There is also a dense expression of sst_2 receptors in the PVN with neuronal localization supporting both pre- and post-synaptic actions (Csaba et al., 2003; Dournaud et al., 1996). Moreover, the inhibitory action of somatostatin on GABA transmission is well documented (Kumar and Grant, 2010). Therefore, it may be speculated that the activation of sst_2 pathways may reduce the tonic GABAergic inhibitory influence on the angiotensin system that drives drinking (Tanaka et al., 2003).

A recent study demonstrated that the dipsogenic response to icv injection of the pan-somatostatin agonist, ODT8-SST is also blocked by the icv OX_1 antagonist, SB-334867 in rats with access to food post injection (Karasawa et al., 2014b). Orexin A can exert dipsogenesis in the absence of food upon icv injection (Kunii et al., 1999). However, as the orexin pathway is also part of the orexigenic circuitry of brain sst_2 activation, the role of OX_1 signaling in the stimulation of drinking induced by activation of sst_2 receptors still needs to be ascertained in the absence of food. In summary, brain somatostatin/cortistatin exerts a rapid in onset dipsogenic response *via* the activation of an sst_2-AT_1 signaling pathway most likely taking place within the PVN.

Role of brain somatostatin 2 receptor signaling in nocturnal feeding and drinking

One recent study indicates the physiological relevance of sst_2 signaling in the diurnal regulation of food intake in rats, namely in the nocturnal feeding behavior, when rodents show their maximal food consumption. The sst_2 antagonist, S-406-028 injected icv reduced the cumulative dark phase food intake at 5 h and 14 h post injection by 27% and 29%, respectively in rats, while having no effect during the light phase (Stengel et al., 2010c). However, under other conditions of stimulated food intake by acute tail pinch in the light phase, the sst_2 antagonist injected icv did not alter the robust feeding response in rats (Goebel-Stengel et al., 2014).

Importantly, the activation of brain sst_2 contributes to the early nocturnal water intake. There is indeed a nocturnal pattern of water ingestion in rats that is well established to be independent of food intake (Karasawa et al., 2014a; Oatley, 1971). First evidence shows that somatostatin and cortistatin-14 injected at low doses devoid of orexigenic effects stimulate water intake resulting in a consumption similar to that occurring spontaneously during the first hours of the dark phase (Karasawa et al., 2014a). Furthermore, the sst_2 antagonist, S-406-028 injected icv inhibited the stimulated water intake observed during the dark phase by >50 %, an effect that lasted over a period of three hours (Karasawa et al., 2014a). Lastly, consistent reports showed that hypothalamic somatostatin content and release are subject to a circadian rhythm with a peak of peptide release at the beginning of the dark phase while lowest levels are observed in the early light phase (Gardi et al., 1999; Ishikawa et al., 1997; Shinohara et al., 1991). In summary, brain somatostatin signaling is likely to be primarily involved in the physiological regulation of nocturnal water intake and to contribute partly to dark phase feeding in rats.

Modulation of stress-related decrease in food intake by somatostatin agonists

Various conditions of acute stress, such as exposure to nociceptive stimuli, immobilization, handling or low doses of endotoxin lead to an increase of hypothalamic somatostatin mRNA expression and peptide release in the median eminence in rats (Arancibia et al., 1984; Arancibia et al., 2000; Priego et al., 2005). The enhanced somatostatin release under conditions of acute stress is further supported by the finding of reduced peptide content in the supraoptic nucleus and the PVN, the locus coeruleus and nucleus of the solitary tract in the rat brainstem (Arancibia et al., 2000; Negro-Vilar and Saavedra, 1980). Likewise, in lambs the stress of maternal separation enhanced somatostatin concentration in nerve terminals of the median eminence (Polkowska and Wankowska, 2010). Other studies also showed that rats exposed to an elevated plus maze displayed activation of somatostatin neurons in the basolateral amygdala (Butler et al., 2012). Lastly, predator stress up-regulates the expression of sst_2 mRNA in the anterior cingulate cortex and the amygdala (Nanda et al., 2008).

In rodents, most stressors including psychological (e.g. acute restraint or emotional stress), somatic (e.g. abdominal surgery) or immunological (e.g. injection of the endotoxin lipopolysaccharide) reduce food intake during the post stress-period through – at least in part – the activation of brain corticotropin releasing factor (CRF) receptors in rats (Hotta et al., 1999; Krahn et al., 1986; Sekino et al., 2004; Shibasaki et al., 1988b; Stengel and Taché, 2014a). Convergent pharmacological reports indicate that the activation of brain sst_2 signaling can prevent the stress-related suppression of food intake. Indeed, earlier studies showed that icv injection of somatostatin-14, somatostatin-28 or octreotide blunted the reduction of food intake induced by restraint (Somiya and Tonoue, 1984) and suppressed the anorexigenic action of CRF (Shibasaki et al., 1988a). Furthermore, the pan-somatostatin agonist, ODT8-SST or a selective sst_2 agonist injected icv completely abolished the inhibition of food intake observed at 2, 4 and 9 h after abdominal surgery in rats, resulting in a normalization of food consumption through a sst_2 mediated action (Stengel et al., 2011). Although ghrelin, a major stimulator of food intake, is reduced by abdominal surgery and restored by icv injection of the stable somatostatin agonist, ODT8-SST (Stengel and Taché, 2012), the additional blockade of the ghrelin receptor under these conditions did not alter the orexigenic effect of the pan-somatostatin agonist, ODT8-SST after abdominal surgery (Stengel et al., 2011). Collectively, stress-related activation of brain somatostatin expression and release along with pharmacological evidence that the activation of somatostatin receptors counteracts the anorexic response to acute stressors support a modulatory role of brain sst_2 signaling in the stress response (Stengel et al., 2013). Further studies are required to assess whether brain somatostatin-sst_2 signaling plays a physiological role in modulating the response to stress through CRF, the hallmark transmitter of the stress response (Stengel and Taché, 2014a).

Summary

Somatostatin and its five receptors are widely expressed in the brain with specific expression patterns indicating the involvement in various homeostatic processes. Early on, a central action of somatostatin administered at low doses to stimulate food intake has been reported. The development of selective sst agonists and antagonists recently allowed the characterization of receptors involved, highlighting a prominent role of the sst_2 for the orexigenic action of brain somatostatin in rodents. Activation of sst_2 signaling recruits a series of orexigenic pathways involving μ-opioid, OX_1, and NPY_1 receptors (Fig. 1) and the inhibition of leptin signaling. Recent studies also point towards a rapid and robust dipsogenic response following the activation of brain sst_2. The stimulation of drinking behavior occurs independently of the orexigenic action and involves angiotensin II-AT_1 signaling. The brain somatostatin-sst_2 signaling contributes in part to nocturnal eating and more importantly to the water consumption. Pharmacological activation of brain sst_2 also prevents visceral stress-related inhibition of food intake, e.g. during postoperative gastric ileus known to involve CRF (Stengel and Taché, 2014b) adding to existing evidence that brain somatostatin counteracts several functional responses to acute stressors by interacting with CRF (Stengel et al., 2013).

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Highlights

- Besides regulation of growth hormone, somatostatin affects several homeostatic systems
- Somatostatin interacts with five somatostatin receptors (sst1-5)
- Brain somatostatin exerts a robust orexigenic effect
- Independent from its orexigenic actions, brain somatostatin also exerts a dipsogenic effect
- Somatostatin counterbalances the response to stress

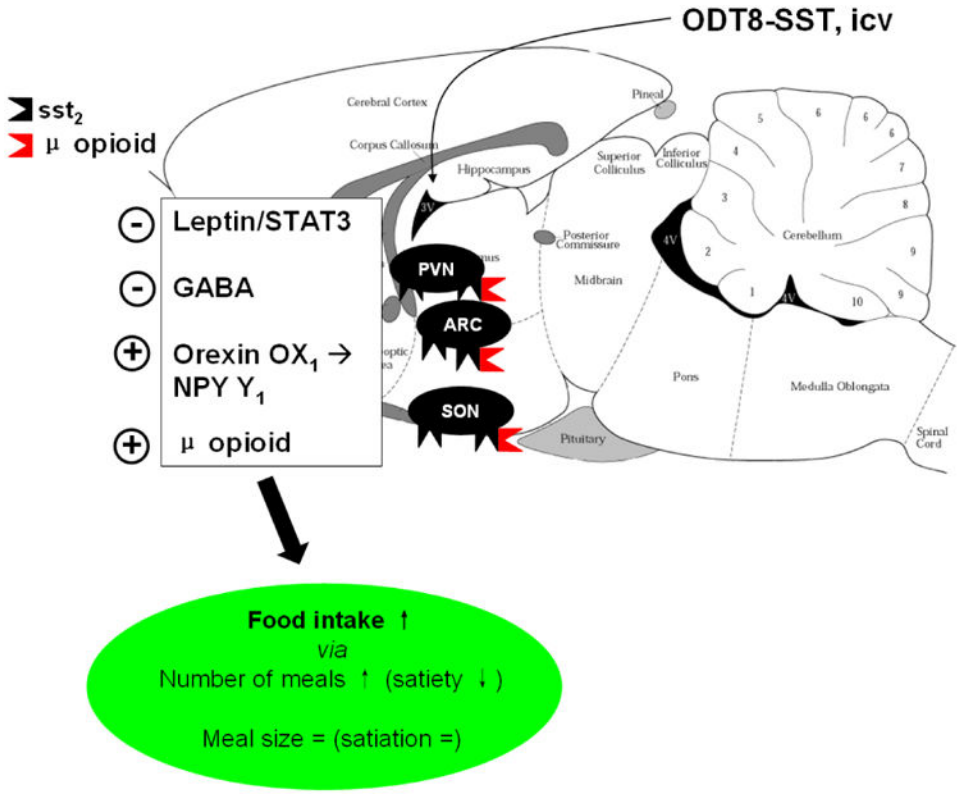

Figure 1.

Suggested downstream hypothalamic circuitries involved in the somatostatin-sst_2 signaling-induced orexigenic response.

The stable pan-somatostatin agonist, ODT8-SST increases food intake *via* activation of sst_2 receptors, an action that involves a downstream stimulation of orexin OX_1 ➔ NPY Y_1 signaling and also μ opioid receptors, indicating an involvement of the rewarding aspect of food. A dimerization of sst_2 and μ opioid receptors might be involved, although the functional relevance of this phenomenon remains to be further characterized. On the other hand, an inhibition of leptin as well as GABA signaling is also likely to contribute to somatostatin's orexigenic effect. Abbreviations: ↓ decrease; ↑ increase; - inhibition; + stimulation; ARC, arcuate nucleus; GABA, gamma-aminobutyric acid; icv, intracerebroventricular; PVN, paraventricular nucleus of the hypothalamus; SON; supraoptic nucleus; sst_2, somatostatin receptor 2; STAT3, signal transducer and activator of transcription 3.

Table 1

Amino acid sequence and receptor binding affinity of somatostatin and sst ligands listed in the order of appearance in this review.

Peptide[Reference]	Structure	Receptor binding affinity (IC_{50}, nM)[a]				
		sst_1	sst_2	sst_3	sst_4	sst_5
somatostatin-14 (SST-14) (Viollet et al., 1995)	Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cy s]-OH	0.1 – 1.5	1.7	1.7	1.0 – 1.6	0.2 – 2.2
somatostatin-28 (SST-28) (Viollet et al., 1995)	Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys]-OH	0.1 – 4.7	0.4 – 5.2	0.2	0.3 – 1.1	0.05 – 0.19
ODT8-SST (Erchegyi et al., 2008)	des-$AA^{1,2,4,5,12,13}$-($DTrp^8$)-SST	27.0 ± 3.4	41.0 ± 8.7	13.0 ±3.2	1.8 ± 0.7	46.0 ± 27.0
octreotide (Grace et al., 2008)	H-(D)-Phe^2-c[Cys^3-Phe^7-$DTrp^8$-Lys^9-Thr^{10}-Cys^{14}]-Thr^{15}(ol)	> 1K	1.9 ± 0.3	39 ± 14	> 1K	5.1 ± 1.1
sst_2 agonist (compound 2, S-346-011) (Grace et al., 2006)	des-$AA^{1,4\text{-}6,11\text{-}13}$-[$DPhe^2$,$Aph^7$(Cbm),$DTrp^8$]-Cbm-SST-Thr-$NH_2$	> 1K	7.5 - 20	942 -1094	872 -957	109 -260
sst_1 agonist (compound 25, S-406-062) (Erchegyi et al., 2009)	des-$AA^{1,4\text{-}6,10,12,13}$-[$DTyr^2$,D-Agl(NMe,2naphtoyl)^8,$IAmp^9$]-SST-Thr-$NH_2$	0.19 ± 0.04	> 1K	158.0 ± 14.0	27.0 ± 7.5	> 1K
sst_4 agonist (compound 15, S-315-297) (Erchegyi et al., 2003)	des-$AA^{1,2,4,5,12,13}$-[Aph^7]-Cbm-SST	650 ± 115	> 1K	780 ± 62	1.5 ± 0.07	> 1K
sst_2 antagonist (compound 4, S-406-028) (Cescato et al., 2008)	des-$AA^{1,4\text{-}6,11\text{-}13}$-[$pNO_2$-$Phe^2$,$DCys^3$,$Tyr^7$,DAph(Cbm)^8]-SST-2Nal-$NH_2$	> 1K	2.6 ± 0.7	384.0 ± 97.0	> 1K	> 1K

Affinities are derived from competitive radioligand displacement assays in cells stably expressing the cloned human receptor using ^{125}I-[Leu^{8}DTrp^{22}Tyr^{25}]SRIF-28 (Cescato et al., 2008; Erchegyi et al., 2003; Erchegyi et al., 2008; Erchegyi et al., 2009; Grace et al., 2006; Grace et al., 2008) except for somatostatin-14 (Viollet et al., 1995) and somatostatin-28 (Viollet et al., 1995).

Table 2

Studies investigating the central effect of somatostatin and its analogues on food intake.

Somatostatin ligand	Dose	Route of injection	Species	Feeding status	Photo-period	Effect on food intake	Duration of action	Reference
Somatostatin-14	0.6 nmol	dorsal hippocampal infusions	rat	not specified	not specified	voracious and prolonged eating	not specified	(Rezek et al., 1976)
Somatostatin-14	0.5 and 2 nmol	icv injection	chick	*ad libitum* fed or 3-h fasted	continuous light	increase	1 h	(Tachibana et al., 2009)
Octreotide	4.9 nmol/d	icv infusion	rat	*ad libitum* fed	light/dark	increase	24 h	(Danguir, 1988)
Octreotide	0.1 nmol	icv injection	rat	*ad libitum* fed	light	increase	40 min	(Beranek et al., 1999)
Octreotide	0.3 and 1 nmol	icv injection	mouse	*ad libitum* fed	light	increase	4 h	(Stengel et al., 2010b)
Somatostatin-14	0.4 – 40 pmol	icv injection	rat	*ad libitum* fed	light/dark	increase of light phase food intake, no effect during the dark phase	1 h	(Feifel and Vaccarino, 1990)
Somatostatin (length not specified)	1 pmol	microinjection into anterior piriform cortex	rat	*ad libitum* fed	dark	increase	3 h	(Cummings et al., 1998)
ODT8-SST	0.3 – 1 nmol	icv injection	rat	*ad libitum* fed	light/dark	increase of light and dark phase food intake	4 h	(Stengel et al., 2010a)
Somatostatin-14	9.8 nmol	icv infusion	rat	rats with restricted feeding schedule (2 h/day)	dark	increase of food intake followed by decrease	1 h	(Aponte et al., 1984)
Somatostatin-14	3 nmol	third ventricle injection	rat	overnight fasted	light	decrease	1 h	(Vijayan and McCann, 1977)
Somatostatin (length not specified)	0.3 – 0.9 nmol	lateral hypothalamus infusion	rat	*ad libitum* fed	light/dark	decrease	24 h	(Lin et al., 1987)
Somatostatin-14	3 nmol	icv injection	rat	*ad libitum* fed	light	decrease	1 h	(Feifel and Vaccarino, 1990)
Somatostatin (length not specified)	2 nmol	microinjection into anterior piriform cortex	rat	*ad libitum* fed	dark	decrease	12 h	(Cummings et al., 1998)
Somatostatin (length not specified)	0.5 – 1 nmol	icv injection	mouse	*ad libitum* fed	light/dark	decrease of 24-h food intake	24 h	(Nakahara et al., 2012)

Abbreviations: icv, intracerebroventricular