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Central somatostatin signaling and regulation of food intake

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Abstract

The discovery of somatostatin (SST) in the hypothalamus implicated the peptide in the inhibition of growth hormone release. However, as observed for numerous neuropeptides, SST was neither restricted to this one brain site nor to this one function. Subsequent studies established a widespread but specific expression of SST in the central nervous system of rodents and humans along with the expression patterns of five receptors ($sst_{1–5}$). Among biological actions, the activation of central SST signaling induced a robust stimulation of food and water intake, which is mediated by the sst_2 as assessed using selective sst agonists. The past years witnessed the identification of brain SST circuitries involved using chemogenetic and optogenetic approaches and further established a physiological orexigenic role of brain SST signaling. The present review will discuss these recent findings.

Graphical abstract:

The current review will present the latest development on the food intake−modulating effects of central somatostatin signaling and brain circuitries involved.

Keywords

brain−gut; drinking; feeding; food intake microstructure; homeostasis

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Competing interests

The authors declare no competing interests.

Introduction

Somatostatin (SST)-14 is a 14-amino-acid peptide first detected in the hypothalamus and shown to induce a robust inhibition of pituitary growth hormone (GH) secretion.[1] Subsequently, SST-28 was identified in the intestine,[2] as the N-terminally extended SST-14 form derived from the same prohormone, pro-SST.[3] Both, SST-14 and SST-28 bind to all five SST receptors ($sst_{1–5}$) with similar affinity.[4, 5] SST receptors are members of the G protein–coupled seven transmembrane domain receptor family.[6] In addition, few sst isoforms have been identified including the full-length sst_{2a} and the truncated form, sst_{2b} in rodents[7] along with several truncated sst_5 variants in rodents and humans.[8, 9] These isoforms can modulate sst_2 signaling[10] and were shown to play a role in different types of cancer.[11–13]

Besides its inhibitory action on GH secretion, numerous brain-initiated extrapituitary effects of SST receptors and/or agonists have been described, such as an increase in blood pressure,[14] blood glucose, body temperature, gastric acid secretion,[15] and gastrointestinal propulsive motor function[16, 17] pointing towards a pleiotropic role of the peptide in line with its widespread brain distribution.[18] Moreover, SST influences behavior increasing grooming,[19] locomotor activity,[20] and anxiety.[21] Brain SST was also early on reported to alter feeding behavior in rodents.[22] Subsequent studies identified the receptor(s) involved using selective peptide sst agonists and antagonists[23] and distinguished between pharmacological and physiological effects.[24] The current review will present the latest development on the food intake–modulating effects of central SST signaling and brain circuitries involved.

Central expression of SST and its receptors

SST displays a wide distribution in the rodent brain with strong immunoreactive signals detected using antibodies recognizing both, Sst-14 and Sst-28.[25] Brain areas encompass those that have been implicated in feeding regulation namely the hypothalamic arcuate (Arc), ventromedial, periventricular, lateral, and paraventricular (PVN) nuclei, the tuberal nucleus (TN), and the nucleus of the solitary tract (NTS).[18, 25–29] SST neurons are also localized in the basal forebrain and mapping of SST projections showed input to other brain areas influencing food intake, such as the lateral hypothalamic area (LHA).[30] Recent studies using a droplet-based single-cell RNA sequencing strategy allowed the identification of four distinct SST neuronal populations in the LHA, which are transcriptionally distinct.[29]

Along with the ligand, are widely expressed in the rodent brain.[6] In food intake–regulatory nuclei, sst expression was localized in the Arc ($sst_1 = sst_{2a} = sst_3 > sst_4$), ventromedial hypothalamic nucleus ($sst_1 > sst_3 > sst_2$), dorsomedial hypothalamic nucleus ($sst_1 = sst_3$), PVN ($sst_{2a} = sst_3$), NTS ($sst_1 = sst_2 > sst_3$), and the dorsal motor nucleus of the vagus ($sst_{2a/b} = sst_4 > sst_5$).[31–35] Expression of both ligand and receptor—predominantly sst_2 and sst_3—in major food intake–regulatory nuclei, such as the Arc, LHA, PVN, and NTS, provides support for an autocrine/paracrine mode of action.

Orexigenic effect of central SST signaling

Over three decades ago, reports indicated that SST-14 or the $sst_{2,3,5}$ agonist, octreotide injected intracerebroventricularly (i.c.v.), into the dorsal hippocampus or anterior piriform

cortex stimulates food intake in rats.[36–40] More recently, the pan-SST agonist, ODT8-SST injected i.c.v. at a low (0.3 nmol) dose led to a pronounced stimulation of food intake not only in the light phase but also in the dark phase—where food intake is already stimulated by other transmitters/hormones—under *ad libitum* conditions in rats and mice.[41–43] While the stimulation of food intake was observed rapidly after i.c.v. injection of octreotide (within 10 min),[36] it was delayed in onset (within 60 min) and longer lasting following i.c.v. ODT8-SST.[41] The i.c.v. ODT8-SST–induced orexigenic effect was associated with a sustained increase in the respiratory quotient and energy expenditure likely contributing to the observed body weight loss 24 h post injection.[41] It is to note that in contrast to the orexigenic effect observed following injection of low doses, higher SST doses in the nmol range injected i.c.v. resulted in an inhibition of food intake in rats and mice[38,44–46] likely related to the induction of other behaviors, such as barrel rotations,[47] but also a leakage/transport into the peripheral circulation[48] where SST predominantly has an anorexigenic effect.[49]

Further studies investigated the SST receptor(s) involved in this orexigenic action. As described above, the $sst_{2,3,5}$ agonist octreotide injected i.c.v. induced a robust increase of light phase food intake in rats[36, 37] and mice.[50] Similarly, the selective sst_2 agonist, S-346–011 injected i.c.v. also stimulated food consumption in rodents, whereas the sst_1 agonist, S-406–062 and sst_4 agonist, S-315–297 did not.[50, 51] Conversely, the orexigenic effect of ODT8-SST was abolished by the selective sst_2 antagonist, S-406–028[41] clearly pointing towards an sst_2-mediated signaling.[50, 51]

Analysis of the underlying food intake microstructure using an automated food intake monitoring system for solid food in undisturbed rodents showed that i.c.v. injection of the sst_2 agonist, S-346–011 increased the number of meals and reduced intermeal intervals during a 4-h period, whereas not altering meal size compared to controls.[50] This is indicative of the suppression of satiety, a mechanism causing a delayed onset of the next meal after completing a meal as reflected by longer intermeal intervals, whereas satiation, a mechanism causing the termination of a meal, was unaltered.[52]

The stimulation of food intake by central activation of SST signaling is likely to be of physiological significance since the sst_2 antagonist, S-406–028 reduced dark phase food intake—when rodents show their highest food intake[53]—by ~30% in rats.[51] In contrast, when injected during the light phase under *ad libitum* feeding conditions, the sst_2 antagonist had no effect on food intake[51] implying the recruitment of Sst–sst signaling to stimulate food intake during the dark photoperiod. This is also supported by a higher hypothalamic Arc[54] and reduced PVN[55] *Sst* mRNA expression in rats housed under conditions of a sustained dark photoperiod along with increased hypothalamic Sst release at the beginning of the dark phase.[56–58]

A recent study provided convergent evidence that SST in the TN plays a physiological role to regulate food intake.[28] First, either fasting or intraperitoneal (i.p.) injection of ghrelin, a hormone released during the hunger state,[59] induced a robust expression of the immediate early gene c-Fos in TN SST neurons.[28] Second, chemogenetic studies further established that activation of SST neurons in the TN promoted a robust food consumption for the

subsequent 3 h by enhancing eating time and frequency.[28] Conversely, optogenetic inhibition of SST neurons in the TN reduced cumulative eating time and frequency.[28] Lastly, selective ablation of these SST neurons resulted in a mild reduction of daily and dark cycle food intake and respiratory exchange ratio.[28]

New developments also unraveled the implication of a population of lateral septum SST-neuronal pathways in facilitating food-seeking behavior.[60] Optogenetic gamma-frequency stimulation of SST-positive lateral septum cells projecting to the LHA induced a specific food-seeking behavior in mice as indicated by a shortened latency to reach the food zone, while not stimulating food intake per se.[60] Interestingly, when the LHA was directly stimulated using optogenetics food intake was increased.[60] These, at first sight, conflicting results have been explained by the differential pattern of activation. Optogenetic stimulation of the lateral septum to LHA projections stimulated the firing of food zone mismatch (cells preferentially active at a distance from the food zone) and less so of food zone match (LH neurons in the free-access feeding model matching the location of the food zone) cells. Conversely, direct activation of the LHA induced the opposite pattern (predominant firing of food zone match neurons).[60] Further chemogenetic approaches in Sst-Cre mice established that selective activation of SST neurons in LHA increases eating behavior.[29]

Other optogenetic and adeno-associated viral tracing studies in mice discovered the involvement of basal forebrain Sst in mediating palatable food consumption.[30] The authors demonstrated that the activation of basal forebrain SST neurons induces selective consumption of high-calorie palatable food (high-fat and high-sucrose) without affecting normal food intake, suggesting that SST neurons in the basal forebrain are involved in hedonic feeding. By contrast, stimulation of projections from SST neurons in the ventral forebrain to the LHA selectively induced fat intake.[30] It is to note that the sst_2 antagonist had no modulating effect on tail pinch–induced food intake,[61] a model to reliably and rapidly stimulate food consumption of regular chow.[62] In view of recent evidence that SST signaling in the basal forebrain may be involved in increasing consumption of high-calorie food,[30] it will be relevant to establish whether sst_2 signaling will counteract the stress-related increase of comfort food consumption.[63, 64]

To investigate downstream signaling pathways involved in the orexigenic effect of central SST several pharmacological studies have been performed. Peripheral injection of the μ-opioid receptor antagonist, naloxone[65] blocked the orexigenic effect of i.c.v. ODT8-SST in rats.[41] Similarly, in chicks, β-funaltrexamine, another μ antagonist prevented the i.c.v. SST–induced orexigenic effect, while δ or κ antagonists did not.[66] The interaction between SST and opioid signaling might happen at the cellular level as the sst_2 was shown to heterodimerize with the μ-opioid receptor.[67] It is to note that functional consequences of this heterodimerization are still to be unraveled.

Moreover, neuropeptide Y (NPY) and orexin signaling are involved in mediating SST's effect on food intake. I.c.v. injection of the NPY1 receptor antagonist, BIBP-3226[68] or the orexin type 1 receptor (OX1) antagonist, SB-334867[69] prevented the food intake–stimulating action of i.c.v. ODT8-SST.[41, 43] The finding that the sst_2 antagonist, S-406–028 did not block the food intake stimulated by orexin-A[43] points towards an SST →sst_2 →OX1

route of signaling. In addition, NPY1 signaling in the Arc was shown to be involved in the downstream mediation of orexin A's–induced food intake–stimulatory effects.[70] This was shown by the blunting of the orexigenic effect of orexin-A by an i.c.v. injected NPY1 antagonist.[71] Moreover, there is neuroanatomical evidence that orexin-expressing neurons in the LHA project to NPY positive neurons in the Arc[72] to activate these neurons.[73, 74] Taken together, SST is likely to mediate its orexigenic action *via* an sst_2 → orexin-A-OX1 → NPY-Y1 pathway.

Dipsogenic effect of central SST signaling

In line with the observed orexigenic effect, the $sst_{2,3,5}$ agonist, octreotide was also shown to induce water intake. This increase was rapid in onset (within 10 min) and not subsequent to the stimulation of food intake since water intake was increased in the absence of food.[75, 76] This observation is consistent with a previous study reporting that the dipsogenic response preceded the orexigenic effect.[36] The dipsogenic response was also established following i.c.v. injection of ODT8-SST, SST-14, and cortistatin,[42] another endogenous sst_{1-5} agonist.[77] While the endogenous ligands, SST-14 and cortistatin exerted short-lasting effects (10 min), ODT8-SST induced a long-lasting (60 min) dipsogenic response.[42]

Similar to the orexigenic effect, the stimulation of water intake is likely mediated *via* the sst_2. This is based on the observation that the selective sst_2 agonist, S-346–011 injected i.c.v. increased water intake to a similar extent as i.c.v. ODT8-SST or cortistatin, while the sst_1 agonist, S-406–062 and the sst_4 agonist, S-315–297 had no effect.[42] Conversely, i.c.v. injection of the sst_2 antagonist, S-406–028 blocked the dipsogenic effect of the pan-sst agonists, cortistatin and ODT8-SST.[42] Sst_2 signaling has physiological relevance in the regulation of drinking behavior as the sst_2 antagonist, S-406–028 injected i.c.v. reduced dark phase—the photoperiod when rats usually drink even independently of food intake[78]—water intake by ~50%.[42] Lastly, SST-14 and cortistatin injected i.c.v. increased water intake to a similar extent observed during the first hours of the dark phase.[42]

The sst_2-mediated dipsogenic response is likely to involve downstream angiotensin II–angiotensin-1 receptor (AT1) signaling as i.c.v. injected losartan, an AT1 antagonist, prevented the dipsogenic response to i.c.v. ODT8-SST, while an sst_2 antagonist did not alter the angiotensin II–induced dipsogenic response.[42] In addition, octreotide was shown to stimulate the release of angiotensin I in the rat hypothalamus pointing towards a physiological cascade.[79]

Another study showed the blockage of the dipsogenic response to ODT8-SST by i.c.v. injection of the OX1 antagonist, SB-334867 in the presence of food,[43] possibly linking the SST-induced downstream food intake- and water intake–stimulatory effect with orexin signaling. A possible dissociation should be further investigated in the absence of food.

Summary

SST is widely expressed in the brain at the level of the ligands as well as the receptors in specific brain areas regulating feeding behavior. The stimulation of food intake by SST has been described early on, a finding confirmed and expanded by independent groups. The

effect is mediated by the sst_2 as assessed using selective agonists and antagonists. Converging evidence points towards the physiological relevance of central Sst–sst_2 signaling to contribute to the orexigenic and dipsogenic responses during the dark phase in rodents. Chemo- and optogenetic approaches along with adeno-associated viral tracing have delineated new SST circuitries in the ventral forebrain, TN and LHA involved in the orexigenic effect and high-calorie food consumption (Fig. 1). The recruitment of these novel SST signaling circuitries warrants further investigations to assess whether they are implicated under stress-related comfort food–seeking conditions.

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References

1. Brazeau P, Vale W, Burgus R, et al. 1973 Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science. 179: 77–79. [PubMed: 4682131]
2. Pradayrol L, Jornvall H, Mutt V, et al. 1980 N-terminally extended somatostatin: the primary structure of somatostatin-28. FEBS Lett. 109: 55–58. [PubMed: 7353633]
3. Benoit R, Esch F, Bennett HP, et al. 1990 Processing of prosomatostatin. Metabolism. 39: 22–25. [PubMed: 1976214]
4. Patel YC 1999 Somatostatin and its receptor family. Front Neuroendocrinol. 20: 157–198. [PubMed: 10433861]
5. Bruns C, Raulf F, Hoyer D, et al. 1996 Binding properties of somatostatin receptor subtypes. Metabolism. 45: 17–20. [PubMed: 8769372]
6. Olias G, Viollet C, Kusserow H, et al. 2004 Regulation and function of somatostatin receptors. J Neurochem. 89: 1057–1091. [PubMed: 15147500]
7. Cole SL & Schindler M. 2000 Characterisation of somatostatin sst2 receptor splice variants. J Physiol Paris. 94: 217–237. [PubMed: 11088000]
8. Duran-Prado M, Gahete MD, Martinez-Fuentes AJ, et al. 2009 Identification and characterization of two novel truncated but functional isoforms of the somatostatin receptor subtype 5 differentially present in pituitary tumors. J Clin Endocrinol Metab. 94: 2634–2643. [PubMed: 19401364]
9. Cordoba-Chacon J, Gahete MD, Duran-Prado M, et al. 2010 Identification and characterization of new functional truncated variants of somatostatin receptor subtype 5 in rodents. Cell Mol Life Sci. 67: 1147–1163. [PubMed: 20063038]
10. Duran-Prado M, Gahete MD, Delgado-Niebla E, et al. 2012 Truncated variants of pig somatostatin receptor subtype 5 (sst5) act as dominant-negative modulators for sst2-mediated signaling. Am J Physiol Endocrinol Metab. 303: E1325–1334. [PubMed: 23032684]
11. Hormaechea-Agulla D, Jimenez-Vacas JM, Gomez-Gomez E, et al. 2017 The oncogenic role of the spliced somatostatin receptor sst5TMD4 variant in prostate cancer. FASEB J. 31: 4682–4696. [PubMed: 28705809]
12. Sampedro-Nunez M, Luque RM, Ramos-Levi AM, et al. 2016 Presence of sst5TMD4, a truncated splice variant of the somatostatin receptor subtype 5, is associated to features of increased aggressiveness in pancreatic neuroendocrine tumors. Oncotarget. 7: 6593–6608. [PubMed: 26673010]
13. Del Rio-Moreno M, Alors-Perez E, Borges de Souza P, et al. 2019 Peptides derived from the extracellular domain of the somatostatin receptor splicing variant SST5TMD4 increase malignancy in multiple cancer cell types. Transl Res.
14. Brown MR 1988 Somatostatin-28 effects on central nervous system regulation of vasopressin secretion and blood pressure. Neuroendocrinology. 47: 556–562. [PubMed: 2899849]

15. Brown M & Taché Y. 1981 Hypothalamic peptides: central nervous system control of visceral functions. Fed Proc. 40: 2565–2569. [PubMed: 6115772]
16. Martinez V, Rivier J, Coy D, et al. 2000 Intracisternal injection of somatostatin receptor 5-preferring agonists induces a vagal cholinergic stimulation of gastric emptying in rats. J Pharmacol Exp Ther. 293: 1099–1105. [PubMed: 10869415]
17. Stengel A, Goebel-Stengel M, Wang L, et al. 2011 Central somatostatin receptor 1 activation reverses acute stress-related alterations of gastric and colonic motor function in mice. Neurogastroenterol Motil. 23: e223–236. [PubMed: 21564422]
18. Viollet C, Lepousez G, Loudes C, et al. 2008 Somatostatinergic systems in brain: networks and functions. Mol Cell Endocrinol. 286: 75–87. [PubMed: 17997029]
19. Van Wimersma Greidanus TB, Maigret C & Krechting B. 1987 Excessive grooming induced by somatostatin or its analog SMS 201–995. Eur J Pharmacol. 144: 277–285. [PubMed: 2894314]
20. Vecsei L & Widerlov E. 1990 Effects of somatostatin-28 and some of its fragments and analogs on open-field behavior, barrel rotation, and shuttle box learning in rats. Psychoneuroendocrinology. 15: 139–145. [PubMed: 1972798]
21. Scheich B, Gaszner B, Kormos V, et al. 2016 Somatostatin receptor subtype 4 activation is involved in anxiety and depression-like behavior in mouse models. Neuropharmacology. 101: 204–215. [PubMed: 26387439]
22. Feifel D & Vaccarino FJ. 1994 Growth hormone-regulatory peptides (GHRH and somatostatin) and feeding: a model for the integration of central and peripheral function. Neurosci Biobehav Rev. 18: 421–433. [PubMed: 7984360]
23. Erchegyi J, Grace CR, Samant M, et al. 2008 Ring size of somatostatin analogues (ODT-8) modulates receptor selectivity and binding affinity. J Med Chem. 51: 2668–2675. [PubMed: 18410084]
24. Stengel A, Karasawa H & Taché Y. 2015 The role of brain somatostatin receptor 2 in the regulation of feeding and drinking behavior. Horm Behav. 73: 15–22. [PubMed: 26026616]
25. Finley JC, Maderdrut JL, Roger LJ, et al. 1981 The immunocytochemical localization of somatostatin-containing neurons in the rat central nervous system. Neuroscience. 6: 2173–2192. [PubMed: 6120483]
26. Johansson O, Hokfelt T & Elde RP. 1984 Immunohistochemical distribution of somatostatin-like immunoreactivity in the central nervous system of the adult rat. Neuroscience. 13: 265–339. [PubMed: 6514182]
27. Moga MM & Gray TS. 1985 Evidence for corticotropin-releasing factor, neurotensin, and somatostatin in the neural pathway from the central nucleus of the amygdala to the parabrachial nucleus. J Comp Neurol. 241: 275–284. [PubMed: 2868027]
28. Luo SX, Huang J, Li Q, et al. 2018 Regulation of feeding by somatostatin neurons in the tuberal nucleus. Science. 361: 76–81. [PubMed: 29976824]
29. Mickelsen LE, Bolisetty M, Chimileski BR, et al. 2019 Single-cell transcriptomic analysis of the lateral hypothalamic area reveals molecularly distinct populations of inhibitory and excitatory neurons. Nat Neurosci. 22: 642–656. [PubMed: 30858605]
30. Zhu C, Yao Y, Xiong Y, et al. 2017 Somatostatin neurons in the basal forebrain promote high-calorie food intake. Cell Rep. 20: 112–123. [PubMed: 28683305]
31. Fehlmann D, Langenegger D, Schuepbach E, et al. 2000 Distribution and characterisation of somatostatin receptor mRNA and binding sites in the brain and periphery. J Physiol Paris. 94: 265–281. [PubMed: 11088004]
32. Hannon JP, Petrucci C, Fehlmann D, et al. 2002 Somatostatin sst2 receptor knock-out mice: localisation of sst1–5 receptor mRNA and binding in mouse brain by semi-quantitative RT-PCR, in situ hybridisation histochemistry and receptor autoradiography. Neuropharmacology. 42: 396–413. [PubMed: 11897118]
33. Schindler M, Humphrey PP, Lohrke S, et al. 1999 Immunohistochemical localization of the somatostatin sst2(b) receptor splice variant in the rat central nervous system. Neuroscience. 90: 859–874. [PubMed: 10218786]

34. Schulz S, Handel M, Schreff M, et al. 2000 Localization of five somatostatin receptors in the rat central nervous system using subtype-specific antibodies. J Physiol Paris. 94: 259–264. [PubMed: 11088003]
35. Spary EJ, Maqbool A & Batten TF. 2008 Expression and localisation of somatostatin receptor subtypes sst1-sst5 in areas of the rat medulla oblongata involved in autonomic regulation. J Chem Neuroanat. 35: 49–66. [PubMed: 17646081]
36. Beranek L, Hajdu I, Gardi J, et al. 1999 Central administration of the somatostatin analog octreotide induces captopril-insensitive sleep responses. Am J Physiol. 277: R1297–1304. [PubMed: 10564200]
37. Danguir J 1988 Food intake in rats is increased by intracerebroventricular infusion of the somatostatin analogue SMS 201–995 and is decreased by somatostatin antiserum. Peptides. 9: 211–213. [PubMed: 2896344]
38. Feifel D & Vaccarino FJ. 1990 Central somatostatin: a re-examination of its effects on feeding. Brain Res. 535: 189–194. [PubMed: 1981489]
39. Feifel D, Vaccarino FJ, Rivier J, et al. 1993 Evidence for a common neural mechanism mediating growth hormone-releasing factor-induced and somatostatin-induced feeding. Neuroendocrinology. 57: 299–305. [PubMed: 8099720]
40. Rezek M, Havlicek V, Hughes KR, et al. 1976 Central site of action of somatostatin (SRIF): role of hippocampus. Neuropharmacology. 15: 499–504. [PubMed: 988503]
41. Stengel A, Coskun T, Goebel M, et al. 2010 Central injection of the stable somatostatin analog ODT8-SST induces a somatostatin2 receptor-mediated orexigenic effect: role of neuropeptide Y and opioid signaling pathways in rats. Endocrinology. 151: 4224–4235. [PubMed: 20610566]
42. Karasawa H, Yakabi S, Wang L, et al. 2014 Brain somatostatin receptor 2 mediates the dipsogenic effect of central somatostatin and cortistatin in rats: role in drinking behavior. Am J Physiol Regul Integr Comp Physiol. 307: R793–801. [PubMed: 25031229]
43. Karasawa H, Yakabi S, Wang L, et al. 2014 Orexin-1 receptor mediates the increased food and water intake induced by intracerebroventricular injection of the stable somatostatin pan-agonist, ODT8-SST in rats. Neurosci Lett. 576: 88–92. [PubMed: 24915296]
44. Cummings SL, Truong BG & Gietzen DW. 1998 Neuropeptide Y and somatostatin in the anterior piriform cortex alter intake of amino acid-deficient diets. Peptides. 19: 527–535. [PubMed: 9533641]
45. Lin MT, Chen JJ & Ho LT. 1987 Hypothalamic involvement in the hyperglycemia and satiety actions of somatostatin in rats. Neuroendocrinology. 45: 62–67. [PubMed: 2880308]
46. Nakahara K, Takata S, Ishii A, et al. 2012 Somatostatin is involved in anorexia in mice fed a valine-deficient diet. Amino Acids. 42: 1397–1404. [PubMed: 21293891]
47. Vecsei L, Pavo I, Zsigo J, et al. 1989 Comparative studies of somatostatin-14 and some of its fragments on passive avoidance behavior, open field activity and on barrel rotation phenomenon in rats. Peptides. 10: 1153–1157. [PubMed: 2576124]
48. Tannenbaum GS & Patel YC. 1986 On the fate of centrally administered somatostatin in the rat: massive hypersomatostatinemia resulting from leakage into the peripheral circulation has effects on growth hormone secretion and glucoregulation. Endocrinology. 118: 2137–2143. [PubMed: 2870913]
49. Bray GA 1995 Nutrient intake is modulated by peripheral peptide administration. Obes Res. 3 Suppl 4: 569S–572S. [PubMed: 8697060]
50. Stengel A, Goebel M, Wang L, et al. 2010 Activation of brain somatostatin 2 receptors stimulates feeding in mice: analysis of food intake microstructure. Physiol Behav. 101: 614–622. [PubMed: 20851136]
51. Stengel A, Goebel M, Wang L, et al. 2010 Selective central activation of somatostatin receptor 2 increases food intake, grooming behavior and rectal temperature in rats. J Physiol Pharmacol. 61: 399–407. [PubMed: 20814067]
52. Fekete EM, Inoue K, Zhao Y, et al. 2007 Delayed satiety-like actions and altered feeding microstructure by a selective type 2 corticotropin-releasing factor agonist in rats: intra-hypothalamic urocortin 3 administration reduces food intake by prolonging the post-meal interval. Neuropsychopharmacology. 32: 1052–1068. [PubMed: 17019404]

53. Rosenwasser AM, Boulos Z & Terman M. 1981 Circadian organization of food intake and meal patterns in the rat. Physiol Behav. 27: 33–39. [PubMed: 7267801]
54. Ross AW, Johnson CE, Bell LM, et al. 2009 Divergent regulation of hypothalamic neuropeptide Y and agouti-related protein by photoperiod in F344 rats with differential food intake and growth. J Neuroendocrinol. 21: 610–619. [PubMed: 19490367]
55. Dulcis D, Jamshidi P, Leutgeb S, et al. 2013 Neurotransmitter switching in the adult brain regulates behavior. Science. 340: 449–453. [PubMed: 23620046]
56. Gardi J, Obal F Jr., Fang J, et al. 1999 Diurnal variations and sleep deprivation-induced changes in rat hypothalamic GHRH and somatostatin contents. Am J Physiol. 277: R1339–1344. [PubMed: 10564205]
57. Ishikawa M, Mizobuchi M, Takahashi H, et al. 1997 Somatostatin release as measured by in vivo microdialysis: circadian variation and effect of prolonged food deprivation. Brain Res. 749: 226–231. [PubMed: 9138722]
58. Shinohara K, Isobe Y, Takeuchi J, et al. 1991 Circadian rhythms of somatostatin-immunoreactivity in the suprachiasmatic nucleus of the rat. Neurosci Lett. 129: 59–62. [PubMed: 1681480]
59. Tschöp M, Smiley DL & Heiman ML. 2000 Ghrelin induces adiposity in rodents. Nature. 407: 908–913. [PubMed: 11057670]
60. Carus-Cadavieco M, Gorbati M, Ye L, et al. 2017 Gamma oscillations organize top-down signalling to hypothalamus and enable food seeking. Nature. 542: 232–236. [PubMed: 28146472]
61. Goebel-Stengel M, Stengel A, Wang L, et al. 2014 Orexigenic response to tail pinch: role of brain NPY(1) and corticotropin releasing factor receptors. Am J Physiol Regul Integr Comp Physiol. 306: R164–174. [PubMed: 24338440]
62. Antelman SM & Szechtman H. 1975 Tail pinch induces eating in sated rats which appears to depend on nigrostriatal dopamine. Science. 189: 731–733. [PubMed: 1154024]
63. Adam TC & Epel ES. 2007 Stress, eating and the reward system. Physiol Behav. 91: 449–458. [PubMed: 17543357]
64. Dallman MF, Pecoraro NC & la Fleur SE. 2005 Chronic stress and comfort foods: self-medication and abdominal obesity. Brain Behav Immun. 19: 275–280. [PubMed: 15944067]
65. Bodnar RJ 2004 Endogenous opioids and feeding behavior: a 30-year historical perspective. Peptides. 25: 697–725. [PubMed: 15165728]
66. Tachibana T, Cline MA, Sugahara K, et al. 2009 Central administration of somatostatin stimulates feeding behavior in chicks. Gen Comp Endocrinol. 161: 354–359. [PubMed: 19523380]
67. Duran-Prado M, Malagon MM, Gracia-Navarro F, et al. 2008 Dimerization of G protein-coupled receptors: new avenues for somatostatin receptor signalling, control and functioning. Mol Cell Endocrinol. 286: 63–68. [PubMed: 18242821]
68. O'Shea D, Morgan DG, Meeran K, et al. 1997 Neuropeptide Y induced feeding in the rat is mediated by a novel receptor. Endocrinology. 138: 196–202. [PubMed: 8977404]
69. Smart D, Sabido-David C, Brough SJ, et al. 2001 SB-334867-A: the first selective orexin-1 receptor antagonist. Br J Pharmacol. 132: 1179–1182. [PubMed: 11250867]
70. Yamanaka A, Kunii K, Nambu T, et al. 2000 Orexin-induced food intake involves neuropeptide Y pathway. Brain Res. 859: 404–409. [PubMed: 10719096]
71. Jain MR, Horvath TL, Kalra PS, et al. 2000 Evidence that NPY Y1 receptors are involved in stimulation of feeding by orexins (hypocretins) in sated rats. Regul Pept. 87: 19–24. [PubMed: 10710284]
72. Horvath TL, Diano S & van den Pol AN. 1999 Synaptic interaction between hypocretin (orexin) and neuropeptide Y cells in the rodent and primate hypothalamus: a novel circuit implicated in metabolic and endocrine regulations. J Neurosci. 19: 1072–1087. [PubMed: 9920670]
73. Muroya S, Funahashi H, Yamanaka A, et al. 2004 Orexins (hypocretins) directly interact with neuropeptide Y, POMC and glucose-responsive neurons to regulate Ca 2+ signaling in a reciprocal manner to leptin: orexigenic neuronal pathways in the mediobasal hypothalamus. Eur J Neurosci. 19: 1524–1534. [PubMed: 15066149]
74. van den Top M, Lee K, Whyment AD, et al. 2004 Orexigen-sensitive NPY/AgRP pacemaker neurons in the hypothalamic arcuate nucleus. Nat Neurosci. 7: 493–494. [PubMed: 15097991]

75. Hajdu I, Obal F Jr., Gardi J, et al. 2000 Octreotide-induced drinking, vasopressin, and pressure responses: role of central angiotensin and ACh. Am J Physiol Regul Integr Comp Physiol. 279: R271–277. [PubMed: 10896891]

76. Hajdu I, Szentirmai E, Obal F Jr., et al. 2003 Different brain structures mediate drinking and sleep suppression elicited by the somatostatin analog, octreotide, in rats. Brain Res. 994: 115–123. [PubMed: 14642455]

77. Siehler S, Nunn C, Hannon J, et al. 2008 Pharmacological profile of somatostatin and cortistatin receptors. Mol Cell Endocrinol. 286: 26–34. [PubMed: 18243519]

78. Oatley K 1971 Dissociation of the circadian drinking pattern from eating. Nature. 229: 494–496. [PubMed: 4925211]

79. Gardi J, Szentirmai E, Hajdu I, et al. 2001 The somatostatin analog, octreotide, causes accumulation of growth hormone-releasing hormone and depletion of angiotensin in the rat hypothalamus. Neurosci Lett. 315: 37–40. [PubMed: 11711209]

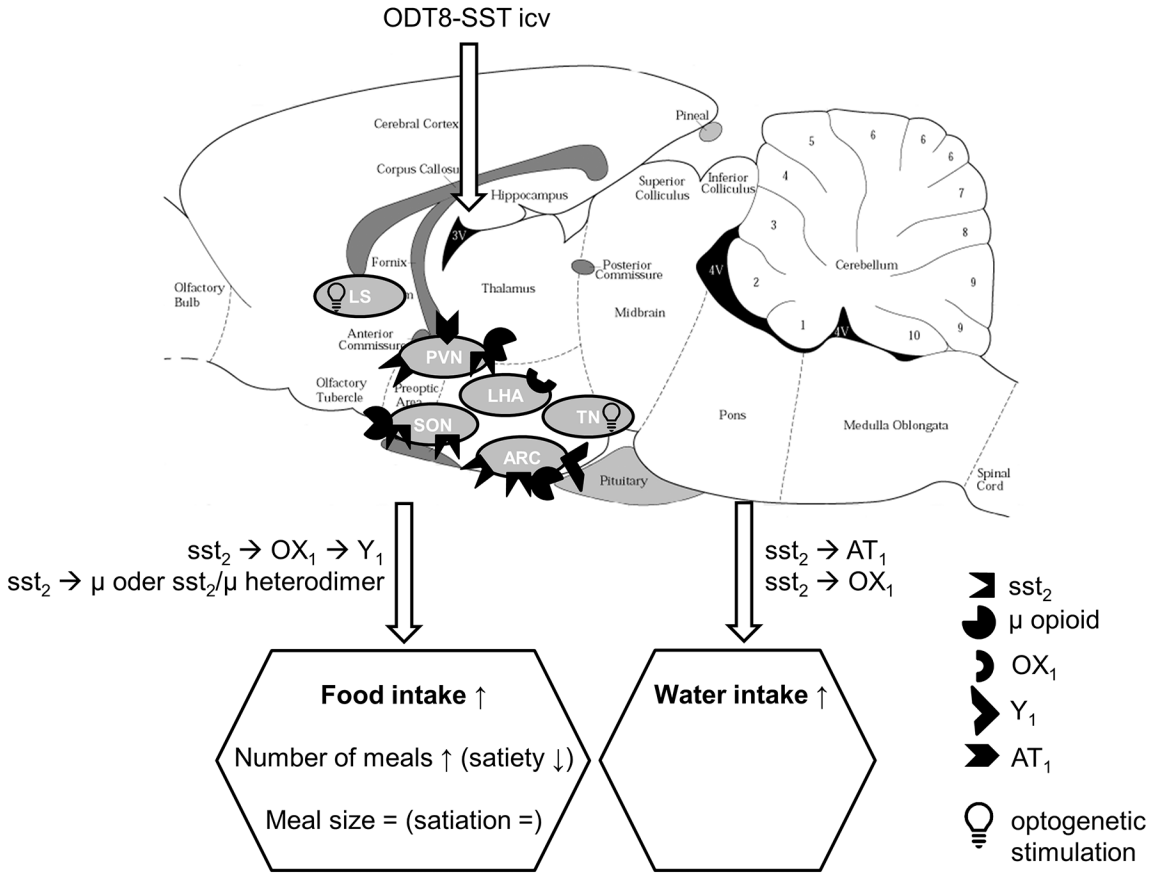

Figure 1.

Mediation of brain SST's orexigenic and dipsogenic effects. Abbreviations: ↑, increase; ↓, decrease; =, no change; μ, μ-opioid receptor; Arc, arcuate nucleus; AT1, angiotensin-II receptor 1; i.c.v., intracerebroventricular; Y_1, LHA, lateral hypothalamic area; LS, lateral septum; NPY1, neuropeptide Y receptor 1; OX1, orexin receptor 1; PVN, paraventricular nucleus; SON, supraoptic nucleus; sst_2, somatostatin receptor 2; TN, tuberal nucleus.