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Modulation of the adaptive response to stress by brain activation of selective somatostatin receptor subtypes

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Abstract

Somatostatin-14 was discovered in 1973 in the hypothalamus as a peptide inhibiting growth hormone release. Somatostatin interacts with five receptor subtypes ($sst_{1–5}$) which are widely distributed in the brain with a distinct, but overlapping, expression pattern. During the last few years, the development of highly selective peptide agonists and antagonists provided new insight to characterize the role of somatostatin receptor subtypes in the pleiotropic actions of somatostatin. Recent evidence in rodents indicates that the activation of selective somatostatin receptor subtypes in the brain blunts stress-CRF related ACTH release ($sst_{2/5}$), sympathetic-adrenal activaton (sst_5), stimulation of colonic motility (sst_1), delayed gastric emptying (sst_5), suppression of food intake (sst_2) and the anxiogenic-like (sst_2) response. These findings suggest that brain somatostatin signaling pathways may play an important role in dampening CRF-mediated endocrine, sympathetic, behavioral and visceral responses to stress.

Keywords

ACTH; anxiety; autonomic nervous system; catecholamines; CRF; food intake; gastrointestinal motility; octreotide; ODT8-SST; stress

1. Introduction

Somatostatin-14 was isolated four decades ago from ovine hypothalamus in the context of a large effort undertaken by Roger Guillemin's group to characterize hypothalamic releasing factors regulating pituitary hormone secretion [7, 40, 41]. The isolated extract inhibited the secretion of growth hormone (GH) from rat pituitary cells *in vitro,* an action that led to the name of the peptide [7]. Subsequently, the N-terminally extended form, somatostatin-28, was identified from the intestine [72]. In addition to the originally described inhibitory effect on GH release, several extrapituitary actions were early on identified in keeping with the

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wide brain distribution of the peptide outside of the hypothalamus soon recognized after its discovery [33, 102]. Namely, somatostatin-28 was reported to act in the brain to influence the autonomic modulation of viscera e.g. the heart rate, blood pressure and gastric acid secretion [10]. Subsequently, important translational developments were based on somatostatin's actions to regulate endocrine functions culminating in the use of somatostatin analogs in neuroendocrine tumor detection [98] and therapy [6]. In addition, during the past few years new advances have been made in rodents to assign a distinct role of somatostatin receptor (sst) subtypes in the brain modulation of the stress response reported early on using the pan-somatostatin agonist des-AA^{1,2,4,5,12,13}-[DTrp^{8}]-somatostatin (ODT8-SST) [34].

In the present review we will focus on recent compelling evidence establishing the central actions of the somatostatin signaling systems to modulate the efferent arms of the response to acute stress encompassing the endocrine, autonomic, visceral and behavioral components through the involvement of distinct somatostatin receptor subtypes. The putative role of somatostatin signaling in modulating the stress response is also supported by the brain distribution of somatostatin and its receptors and their regulation under acute stress conditions along with evidence that somatostatin inhibits hypothalamic corticotropin releasing factor (CRF) which plays a key role in orchestrating the multifaceted stress response [4, 90].

2. Brain somatostatin and somatostatin receptors – distribution and signaling

Somatostatin is widely expressed in the whole rodent brain except the cerebellum [33, 46, 102]. A dense expression is found in deep layers of the cortex, central nucleus of the amygdala, limbic and sensory system, periaqueductal central gray and the hypothalamus where somatostatin is mainly localized in the arcuate, ventromedial and paraventricular (PVN) nuclei [33, 46, 62].

Somatostatin receptors encompass five subtypes ($sst_{1–5}$) belonging to the family of G-protein coupled seven transmembrane domains (TMD) receptors [69]. Spliced variants have been identified for sst_2 and sst_5 including the full length sst_{2a} and the C-terminal truncated shorter isoform referred to as sst_{2b} displaying similar binding affinity to $sst_{1–5}$ [19]. The sst_5 variants are generated by splicing of cryptic introns at the sst_5 mRNA level leading to different numbers of TMD [22, 28]. Specifically, three functional variants have been identified in mouse, named sst_5TMD4, sst_5TMD2 and sst_5TMD1, one in rats (sst_5TMD1) and two in humans, namely sst_5TMD4 and sst_5TMD5. These variants show high inter-species nucleotide and amino acid sequence identity and contain the same N-terminal region as full length sst_5 but bear different, shorter C-terminal tails [22, 28].

Similarly to the ligand, somatostatin receptor subtypes are also widely expressed throughout the brain with specific patterns [69]. Somatostatin receptors are densely expressed in the deep layers of the cerebral cortex ($sst_1 > sst_{2a/b} = sst_3 > sst_4$), bed nucleus of the stria terminalis ($sst_{2a/b} > sst_1 > sst_4$), hippocampus ($sst_1 > sst_{2a,b} = sst_3 > sst_4$), the basolateral amygdaloid nucleus ($sst_{2a/b} > sst_1 = sst_3 > sst_4$), the medial amygdaloid nucleus ($sst_3 > sst_1 = sst_2$), the arcuate nucleus of the hypothalamus ($sst_1 = sst_{2a} = sst_3 > sst_4$), the dorsomedial hypothalamic nucleus ($sst_1 = sst_3$), the ventromedial hypothalamic nucleus ($sst_1 > sst_3 > sst_2$), the PVN ($sst_{2a} = sst_3$), substantia nigra ($sst_3 > sst_1 > sst_{2a/b}$), dorsal raphe nucleus ($sst_1 = sst_2 = sst_3$), the granular layer of the cerebellum ($sst_3 > sst_5 > sst_{2b} > sst_1 = sst_4$), locus coeruleus ($sst_2 > sst_3$), nucleus of the solitary tract ($sst_1 = sst_2 > sst_3$) and the dorsal motor nucleus of the vagus nerve ($sst_{2a/b} = sst_4 > sst_5$) [32, 42, 78, 79, 84]. With regard to the sst_5 expression patterns of truncated sst_5 variants, there is a distinct distribution which is brain area- and variant-dependent. In the mouse hypothalamus and cerebellum, mRNA levels of

sst_5 are the most abundant, followed by sst_5TMD2 and sst_5TMD1, whereas sst_5TMD4 is not detected [22, 42]. By contrast, in the mouse cerebral cortex, full length sst_5 is not detected while all truncated sst_5 variants are present at different levels (sst_5TMD2 >> sst_5TMD4 > sst_5TMD1) supporting a primary role of these variants in the cerebral cortex [22, 42]. Of note, CHO-K1 cells stably transfected with mouse sst_5TMD4 responded exclusively to somatostatin while mouse sst_5TMD2 is mainly activated by cortistatin, a structurally somatostatin-related endogenous peptide, and sst_5TMD1 by both ligands [21, 22]. By contrast, the human sst_5TMD5 responded preferentially to somatostatin while sst_5TMD4 was selectively activated by cortistatin [21, 28]. Although these data showed a species-specificity in their signaling properties, these new variants may convey biological actions that are distinct between somatostatin and cortistatin [21].

Using the immediate early gene *c-fos* as an established marker of neuronal activation [27, 76], several reports showed that somatostatin injected intracerebroventricularly (icv) at a low dose in rats induces Fos protein expression in the supraoptic nucleus, the PVN and in the subfornical organ [58]. Likewise, icv injection of selective agonists, namely the sst_2 agonist, des-AA$^{1,4–6,11–}$-[DPhe^2,Aph^7(Cbm),DTrp^8]-Cbm-SST-Thr-NH_2 [38] (Table 1) and the stable pan-somatostatin agonist, ODT8-SST [31] induce Fos protein in the somatosensory and motor cortex, striatum, basolateral amygdaloid nucleus, ventral premamillary nucleus, supraoptic nucleus, arcuate nucleus, PVN, lateral parabrachial nucleus, inferior olivary nucleus, cerebellum, and caudal spinal trigeminal nucleus in rats [36]. Although similar areas were activated by both peptides injected icv at an equimolar dose, the Fos response following the sst_2 agonist was more pronounced than that induced by icv ODT8-SST [36]. This is likely due to different sst binding affinities between both peptides as ODT8-SST displays a lower affinity to the sst_2 than the selective sst_2 agonist (IC_{50} binding affinity of the sst_2 agonist to the sst_2: 7.5–20 nM [38] compared to 41.0 ± 8.7 nM for ODT8-SST [31]). In addition, ODT8-SST but not the sst_2 agonist displays high affinity to the other four sst subtypes [31] which could also account for the differences in Fos activation observed. Indeed, previous electrophysiological studies demonstrated that somatostatin inhibits neuronal activity in the hypothalamic arcuate nucleus [66], locus coeruleus [18] and periaqueductal gray [20]. Other evidence showed that the sst_2, sst_3 and sst_5 agonist, octreotide reduces Fos expression in the spinal trigeminal nucleus stimulated by corneal manipulation [5]. Overall, among the brain sites responsive to somatostatin or somatostatin agonists, several are relevant to neurocircuitries implicated in the stress response [45, 77].

3. Activation of brain somatostatin release and up-regulation of somatostatin receptors by stress

The stimulation of somatostatin neurons or release under various conditions of acute stress is well established. Exposure to a novel environment such as the elevated plus maze activates somatostatin neurons in the basolateral amygdala [16]. Several types of stressors namely handling, exposure to nociceptive stimuli, immobilization, or low doses of endotoxin increased hypothalamic somatostatin mRNA levels or peptide release from the median eminence in rats [2, 3, 73]. Likewise, in young lambs somatostatin is elevated in nerve terminals of the median eminence after three days of maternal separation [71]. A decrease in peptide content in the hypothalamus (supraoptic nucleus, PVN) and extrahypothalamic areas including the locus coeruleus and nucleus of the solitary tract after acute stress in rats is also indicative of a somatostatin release from those brain nuclei [3, 68]. In line with the observed changes of the ligand, the acute exposure of rats to a potential predator led to an upregulation of sst_2 mRNA expression in the amygdala and the anterior cingulate cortex associated with a robust Fos expression in the amygdala [67].

4. Activation of brain somatostatin signaling modulates the stress response

Exposure to various stressors induces a complex repertoire of endocrine, autonomic, visceral and behavioral responses of the organism. Those changes are largely coordinated by the activation of the CRF signaling system in the brain [4, 90]. Mounting evidence supports that brain activation of somatostatin signaling counteracts the various components of the stress response. This may have a bearing with the associated dampening of hypothalamic CRF release and/or actions suggesting that somatostatin may play an important role in modulating the CRF-mediated physiological response to stress.

4.1. Endocrine responses

4.1.1. Activation of brain $sst_{2,5}$ inhibits stress-related stimulation of hypothalamic CRF and pituitary adrenocorticotropic hormone release—Earlier studies demonstrated that somatostatin-28 (sst affinity displayed in Table 1) injected icv but not iv blocked the increase of circulating adrenocorticotropic hormone (ACTH) stimulated by an acute tail suspension stress [15]. Similarly, the stable pan-somatostatin ODT8-SST (Table 1) induced the same effect, whereas somatostatin-14 did not [15]. Of importance, ODT8-SST did not alter ACTH secretion stimulated by icv injection of CRF indicative of an action on the expression and/or release of CRF induced by stress [15]. This was supported by subsequent *in vitro* studies showing that somatostatin, octreotide or cortistatin reduced the basal and KCl-stimulated release of CRF from hypothalamic and hippocampal explants [100, 101]. By contrast, the release of cortical CRF was stimulated by somatostatin [100] indicating a differential action dependent on the brain region. The receptor subtype mediating somatostatin's action to suppress hypothalamic CRF release is likely to be sst_5 and/or sst_2. This is based on the mimicry between octreotide ($sst_5 = sst_2 > sst_3$ agonist) and somatostatin to inhibit CRF release *in vitro* [101] and the central action of somatostatin-28, which has higher affinity to sst_5 than somatostatin-14, to reduce circulating ACTH in response to acute stress unlike somatostatin-14 [15]. In addition, a direct interaction between CRF and somatostatin occurs also at the hypophyseal level. In AtT-20 cells, a murine model of pituitary corticotropes, somatostatin-14 and −28 and subtype-selective sst_2 or sst_5 agonists inhibited CRF-induced ACTH release while other selective sst subtype agonists had no effect [93]. This is further supported by the expression of sst_2 and sst_5 on pituitary cells at the mRNA and protein level [26, 60]. Moreover, sst_2 knockout mice displayed an increased pituitary ACTH release *in vitro* compared to pituitary ACTH release from wild type littermates [104]. This points towards a crucial role of the sst_2 in the basal inhibition of ACTH, thereby greatly influencing the endocrine response to stress.

4.1.2. Activation of brain sst mediates stress-induced suppression of GH release—The suppression of pituitary GH release was the first biological action ascribed to somatostatin [1]. Convergent evidence demonstrated the involvement of hypothalamic somatostatin in the suppression of GH induced by brain CRF or exposure to stress. CRF injected icv reduces plasma levels of GH, an effect blocked by intravenous (iv) injection of an anti-somatostatin antiserum [47]. Moreover, icv injection of a CRF receptor antagonist inhibited the reduction of circulating GH levels induced by electroshocks in rats [74]. Therefore, with regard to the stress-related GH suppression, data are indicative of CRF recruiting somatostatin and thereby mediating - and not opposing - this endocrine response.

4.2. Sympathetic response

Pioneer studies by Brown et al. established that oligosomatostatin analogs act in the brain to interfere with sympatho-adrenal activation elicited by various acute stressful stimuli in rats

[12]. ODT8-SST [31] or the sst_5=sst_2>sst_3 agonist, octreotide [39] injected icv but not iv prevented psychological/somatic (hanging rats by their tail for 3 min, unexpected noise for 4 min or cold swim for 2 min), chemical (short exposure to ether vapor) and metabolic (iv insulin or 2-deoxy-D-glucose, or icv carbachol or bombesin) stressors-induced rise in plasma levels of adrenaline and - to a lower extent - noradrenaline in rats [15, 34, 37]. Similarly to oligosomatostatin agonists, somatostatin-28 blocked the secretion of adrenaline induced by icv bombesin, while somatostatin-14 was much less potent [9]. In addition, direct assessment of sympathetic outflow using electrophysiological recording in the adrenal branch of the splanchnic nerve showed that icv injection of somatostatin-14 reduced adrenal sympathetic activity in rats [83]. This sympatho-adrenal inhibition was also extended to dogs where icv injected ODT8-SST blocked the elevation of plasma adrenaline in response to icv carbachol [61]. Other studies in dogs established that the dorsal hypothalamic area is a site of somatostatin-28 and ODT8-SST action to inhibit adrenaline secretion induced by icv bombesin [11]. Investigations in rats directed to elucidate potential brain mechanisms showed that icv octreotide suppressed the increased hypothalamic noradrenergic activity induced by iv 2-deoxy-D-glucose or cold swim stress [37]. The brain somatostatin receptor subype(s) involved in blunting the stimulated sympathetic activity are still to be characterized using selective agonists. However, data obtained with octreotide and somatostatin-28 compared to somatostatin-14 [9, 37] may be indicative of an interaction with sst_5 and/or sst_2. Further supporting this assumption, sst_2 and sst_5 are highly expressed in hypothalamic and medullary nuclei regulating sympathetic outflow [32, 42, 79, 84].

There is also evidence that somatostatin may regulate sympathetic basal tone. Depletion of endogenous brain somatostatin by cysteamine increased plasma levels of adrenaline [8] which can be reversed by central injection of ODT8-SST [14] or somatostatin [13]. Retrograde transneuronal tracing studies with pseudorabi virus in rats also provide neuroanatomical support for the regulation of peripheral catecholamine release by brain somatostatin as shown by the multisynaptic connections between the adrenal medulla and somatostatin positive cells located either in the medulla oblongata namely the raphe pallidus, raphe obscurus, ventromedial medulla, A5 or the PVN [84, 92].

4.3. Visceral responses

4.3.1. Activation of brain sst_5 blocks stress-related delayed gastric emptying

—Acute stressors affect gastrointestinal motor functions mainly by inhibiting gastric transit while stimulating colonic transit and propulsive motility in rodents [95]. Likewise, these stress-related gastrointestinal alterations are mimicked by central injection of CRF in naïve rodents and prevented by central injection of CRF receptor antagonists prior to exposure to the stressors supporting a primary role of brain CRF signaling in these responses [23, 53, 57, 94]. On the contrary, somatostatin-28, the pan-somatostatin agonist, ODT8-SST or the sst_5 predominant agonist, BIM-23052 injected into the cisterna magna accelerated gastric emptying of a liquid non-nutrient solution in rats through activation of vagal cholinergic pathways as shown by a complete blockade by subdiaphragmatic vagotomy or atropine in rats [54]. Under the same conditions, intracisternal (ic) injection of somatostatin-14 or the sst_1 (CH-275), sst_2 (DC-32–87), sst_3 (BIM-23056) and sst_4 (L-803,087) preferential agonists had no effect [54] along with systemic injection of ODT8-SST [85] or the sst_5 predominant agonist, BIM-23052 [54]. These data point to a role of brain sst_5 activation which is further supported by neuroanatomical evidence of a prominent sst_5 expression in the dorsal motor nucleus of the vagus nerve [99]. Although the sst_5 seems to play a major role, an interaction with other sst cannot be ruled out since the sst_5 is known to form heterodimers with the sst_1 or sst_2 resulting in a 50-and 10-fold increased signaling efficiency, respectively [75]. Moreover, the sst_5 may also be involved through forming heterodimers with the ghrelin receptor [70]. Activation of ghrelin receptors located in the dorsal vagal complex induces a

vagal dependent increase of gastric antral motility and relaxation of the proximal stomach consistent with increased digestive functions [50]. ODT8-SST injected into the lateral brain ventricle also stimulates gastric emptying of a solid meal in mice [86] and rats [85] and the response was blocked by naloxone [85]. This is indicative of distinct forebrain and hindbrain sites and mechanisms of ODT8-SST action to enhance basal gastric transit in rats which need to be further localized.

In addition to stimulating basal gastric emptying, central injection of somatostatin agonists prevents the acute stress-related inhibition of gastric emptying. Abdominal surgery is known to delay gastric emptying resulting in postoperative gastric ileus, an effect that was completely blocked by the ic injection of ODT8-SST or the sst_5 preferring agonist, BIM-23052 [87]. Moreover, the pan-somatostatin agonist, ODT8-SST injected ic prevented the surgery-induced reduction of circulating ghrelin levels, an effect that was mimicked by the sst_2 agonist but not by sst_1 and sst_4 agonists injected ic [87]. These data indicate that differential brain sst receptor subtypes are involved in restoring gastric emptying and circulating levels of ghrelin inhibited by abdominal surgery. This, along with the demonstration that the ghrelin receptor antagonist, [D-Lys^3]-GHRP-6 injected peripherally did not influence the ic ODT8-SST-induced prevention of postoperative gastric ileus [87], indicates that the normalization of the prokinetic hormone ghrelin does not play a primary role. The prevention of postoperative gastric ileus by ic ODT8-SST may likely be mediated by a direct influence on vagal efferent activity regulating gastric motor function.

4.3.2. Activation of brain sst_1 prevents stress-related activation of colonic motor function—Contrasting with the inhibitory effects on the upper gastrointestinal tract, activation of the brain CRF signaling system stimulates the secretomotor function of the colon in rodents [55–57]. Since sst are expressed in brain nuclei regulating colonic functions [64, 65, 97] including the locus coeruleus ($sst_{2–4}$), arcuate nucleus of the hypothalamus ($sst_{1–5}$) and the PVN ($sst_{2–4}$) [32, 79] in rodents, the effect of somatostatin and sst agonists on stress and brain CRF-induced alterations of propulsive colonic functions has been investigated in a recent study [86]. Acute stress conditions induced by inhalation of a volatile anesthetic followed by icv injection of water robustly stimulates propulsive colonic motor function reflected by a strong increase in fecal pellet output in mice [86]. This effect was completely abolished by the icv injection of ODT8-SST, somatostatin-28 or a selective sst_1 agonist whereas the oligo-somatostatin agonist, octreotide (sst_5=sst_2>sst_3) or selective sst_2 or sst_4 agonists had no effect indicative of a sst_1-mediated mode of action [86]. Similarly, icv injection of CRF or exposure to water avoidance for 1 h induced the stimulation of fecal pellet output [57] which was blocked by the icv injection of ODT8-SST in mice [86]. By contrast, the stimulation of colonic secretomotor functions induced by peripherally initiated activation of colonic myenteric neurons using ip injection of tryptophan [105] was not altered by icv ODT8-SST [86]. Further studies established that ic injection of ODT8-SST blunted the colonic contractile activity assessed non-invasively in the distal colon in mice maintained under semi-restraint conditions [86]. Collectively, these data support a central inhibitory action of somatostatin on acute stress-related stimulation of propulsive colonic motor function likely to involve the sst_1 and a reduction in hypothalamic CRF-related signaling established to play a role in the colonic response induced by various stressors [96].

4.4. Behavioral responses

4.4.1. Activation of brain sst_2 prevents stress-related anorexia—Convergent studies established that various stressors (acute restraint or emotional stress) or icv injection of CRF reduced food intake during the post stress-period through activation of brain CRF receptors in rats [44, 52, 80, 82]. Earlier reports indicate that icv somatostatin-14,

somatostatin-28 or octreotide counteracts the suppressive effect of icv CRF on food intake [81] as well as restraint stress-induced anorexia in rats [82]. More recently, in a model of visceral stress induced by abdominal surgery, the icv injection of ODT8-SST was also found to prevent the decrease in food intake occurring during the post surgery period in rats [87]. This was reproduced by the icv injection of the selective peptide sst_2 agonist pointing towards a sst_2 mediated orexigenic effect to offset the post-surgery disturbance of food consumption [87]. Although the decrease of ghrelin levels induced by abdominal surgery is also prevented by icv ODT8-SST, this restoration of the orexigenic peptide is unlikely to be the exclusive underlying mechanism as the blockade of the ghrelin receptor using a ghrelin receptor antagonist did not alter the icv ODT8-SST induced normalization of food intake after abdominal surgery [87]. It may be speculated that activation of brain sst_2 interferes with the CRF mediated anorexic action of the peptide.

Under basal (light phase) as well as stimulated (dark phase) conditions, the pan-somatostatin agonist, ODT8-SST injected icv at a similar dose as in the stress experiment also increases food intake in rats [85]. Conclusive evidence assigned the sst_2 as the main receptor subtype mediating the orexigenic action of brain somatostatin. Co-injection of a selective peptide sst_2 antagonist completely abolished the orexigenic action induced by icv ODT8-SST in rats [85]. Likewise, the oligo-somatostatin agonist, octreotide, or a highly selective sst_2 peptide agonist (Table 1) injected icv increased food intake in rodents [25, 89]. Conversely, icv injection of a selective peptide sst_2 antagonist at the beginning of the dark phase reduced food intake in freely fed rats [89]. Similarly, blockade of endogenous brain somatostatin signaling by chronic third ventricular infusion of an anti-somatostatin antiserum over two days decreased daily food consumption [25]. Collectively, these data suggest a physiological orexigenic effect of brain somatostatin-sst_2 signaling. In line with this assumption, the sst_2 is robustly expressed in brain nuclei regulating food intake such as the arcuate nucleus of the hypothalamus, PVN, supraoptic nucleus as well as ventromedial and lateral hypothalamus [24, 32, 63, 79, 91]. The orexigenic effect of brain sst_2 activation is characterized by an increased number of meals associated with reduced inter-meal intervals whereas meal sizes were not affected by the sst_2 agonist in mice [88]. Therefore, activation of brain sst_2 signaling increases food intake by inhibiting satiety whereas satiation is not altered [88].

4.4.2. Activation of brain sst_2 prevents stress-related anxiogenic behavior—

Neuroanatomical and functional studies are indicative that brain somatostatin-sst_2 exerts an anxiolytic effect in stress models of anxiety [29, 106, 107]. The sst_2 subtype is densely expressed in brain nuclei implicated in anxiety such as the amygdala, septum, PVN, and hippocampus [43, 49, 51]. Behavioral studies showed that the sst_2 agonist, L-779976 injected icv inhibited anxiety-like behavior induced by exposing rats to the elevated plus-maze, while the agonists to sst_1, L-797591, sst_3, L-796778, sst_4, L-803087 or sst_5, L-817818 had no effect [29]. Brain responsive sites involve the central amygdala and septum [106, 107]. Microinjection of somatostatin-14 and -28 into these brain nuclei results in an anxiolytic-like effect tested in the elevated-plus maze and shock-probe burying test which was reversed by microinfusion of the sst_2 antagonist, PRL2903 at these sites [106, 107]. Cellular mechanisms contributing to somatostatin's action to decrease anxiety behavior have been related to the somatostatin sst_2 mediated action to induce membrane hyperpolarization and a decrease in input resistance, resulting in the reduction of cell excitability in rat amygdala neurons [59]. Moreover, further supporting a role of the sst_2 in counteracting the stress-related anxiogenic response, sst_2 knockout mice display a behavioral profile of marked-anxiety behavior when exposed to various stress-inducing environments, including open-field test, novel cage or elevated plus maze [104]. As sst_2 knockout mice display an enhanced CRF-ACTH release to stress exposure [104] and brain CRF signaling plays a major role in the anxiogenic response to stress [48], the anxiolytic effect of brain sst_2 signaling may also be mediated by the reduction of CRF's anxiogenic action.

5. Conclusions

Somatostatin and the five specific G-protein coupled sst are expressed throughout the brain with specific expression patterns consistent with the importance of somatostatin signaling pathways in the regulation of a number of distinct physiological processes. This involvement is now being better characterized, mainly due to the availability of pharmacological tools such as selective sst agonists and antagonists [17, 30, 31, 38]. Activation of specific sst subtypes in the brain prevents the occurrence of key endocrine, autonomic, visceral and behavioral components of the stress manifestations (Table 2). Mounting evidence showed that the stable pan-somatostatin agonist, ODT8-SST or somatostatin-28 injected into the rodent brain through interaction with specific sst, namely sst_2, sst_5 or sst_1 (Table 2) prevents the acute-stress-induced stimulation of hypothalamic CRF-ACTH release, elevation of circulating catecholamines, slowing of gastric emptying, stimulation of colonic secretomotor function, decrease in food intake and anxiety-like behaviors. Collectively, these reports point to a potential role of brain somatostatin receptors in modulating several processes of the stress response. This is supported by existing evidence that sst_2 knockout mice displayed a heightened ACTH and anxiogenic response to environmental stress [104]. Although the role of endogenous somatostatin-sst_1 and sst_5 signaling systems in dampening the other components of stress-related autonomic and visceral alterations are still to be further assessed, overall the existing evidence supports an important modulatory role of brain somatostatin systems in the stress response. Therefore, the regulation of the relative interaction between brain somatostatin and CRF pathways activated by stressors may be essential in coordinating the various physiological efferent components of stress. In addition, targeting specific sst may open new anti-stress therapeutic venues.

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Research highlights

- Brain activation of sst subtypes blunts various components of the stress response.
- Brain $sst_{2/5}$ inhibits stress-induced CRF-ACTH release.
- Brain sst_2 prevents stress-related anorexia and anxiogenic-like responses
- Brain sst_5 suppresses stress-induced sympathetic activation and gastric stasis.
- Brain sst_1 blocks stress-induced stimulation of colonic motor function.

Table 1

Amino acid sequence and receptor binding affinity of somatostatin and sst agonists listed 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) [103]	Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys]-OH	0.1 – 1.5	1.7	1.7	1.0 – 1.6	0.2 – 2.2
somatostatin-28 (SST-28) [103]	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
octreotide [39]	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
ODT8-SST [31]	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
sst_1 agonist (compound 25) [30]	des-$AA^{1,4–6,10,12,13}$-[$DTyr^2$,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_2 agonist (compound 2) [38]	des-$AA^{1,4–6,11–13}$-[$DPhe^2$,Aph^7(Cbm),$DTrp^8$]-Cbm-SST-Thr-NH_2	> 1K	7.5 – 20	942 – 1094	872 – 957	109 – 260
cortistatin-17 [35]	Asp-Arg-Met-Pro-cyclo-[Cys-Arg-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys]Lys	0.3 – 7.0	0.6 – 0.9	0.4 – 0.6	0.5 – 0.6	0.3 – 0.4

Affinities are derived from competitive radio ligand displacement assays in cells stably expressing the cloned human receptor using ^{125}I-[Leu^{8}DTrp^{22}Tyr^{25}]SRIF-28 [30, 31, 38, 39] except for somatostatin-14 [103], somatostatin-28 [103] and cortistatin [35].

Table 2

Brain somatostatin signaling pathways modulate the acute stress response.

Stressor	Species	Stress Response	Sst agonist Treatment	Effect	Receptor	Reference
		Endocrine				
KCl stimulation	rat hypothalamic and hippocampal explants	↑ CRF	SST-14, octreotide or cortistatin	reduction of CRF release	sst_2 and sst_5	[100, 101]
Tail suspension	rat	↑ ACTH	SST-28 or ODT8-SST icv	blockade of ACTH increase	sst_5 and sst_2	[15]
CRF icv	rat	↓ GH	anti-SST antiserum iv	blockade of GH reduction	$sst_{1–5}$, predominant subtype to be further determined	[47]
		Behavioral				
Abdominal surgery	rat	↓ Feeding	ODT8-SST, sst_2 agonist icv	restoration of food intake	sst_2	[87]
Plus maze test, shockprobes	rat	↑ Anxiety	SST-28 and SST-14 into amygdala or septum	anxiolytic effect	sst_2	[106]
		Autonomic				
Tail suspension	rat	↑ Sympathetic	ODT8-SST or octreotide icv	blockade of rise in adrenaline and noradrenaline	sst_2 and sst_5	[15, 34]
Abdominal surgery	rat	↓ Vagal	BIM-23052 ic	restoration of gastric emptying by ic BIM-23052 is blocked by subdiaphragmatic vagotomy or atropine	sst_5	[54]
		Visceral				
Abdominal surgery	rat	↓ Gastric transit	ODT8-SST or BIM-23052 ic	blockade of postoperative gastric ileus	sst_5	[87]
Short inhalation anesthesia and icv injection of water	mouse	↑ Colonic motor function	ODT8-SST, SST-28 or sst_1 agonist	blockade of secretomotor response	sst_1	[86]

Abbreviations: ic, intracisternal; icv, intracerebroventricular; iv, intravenous; SST, somatostatin; sst, somatostatin receptor