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Review

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-corticotropin-releasing factor (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.

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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 [7,41,42]. 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 [74]. In addition to the originally described inhibitory effect on GH release, several extrapituitary actions were early on identified in keeping with the wide brain distribution of the peptide outside of the hypothalamus soon recognized after its discovery [34,104]. 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 [100] and therapy [6].

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) [35]. 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 [4,92].

2. Brain somatostatin and somatostatin receptors – distribution and signaling

Somatostatin is widely expressed in the whole rodent brain except the cerebellum [34,47,104,105]. 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 [34,47,63].

Somatostatin receptors encompass five subtypes (sst_{1-5}) belonging to the family of G-protein coupled seven transmembrane domain (TMD) receptors [70]. 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 [70]. 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 ($sst_{2a/b} = sst_4 > sst_5$) [33,43,80,81,86]. 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 [22,43]. 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 $\gg$ sst_5TMD4 > sst_5TMD1) supporting a primary role of these variants in the cerebral cortex [22,43]. 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 [27,78], 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 [59]. Likewise, icv injection of selective agonists, namely the sst_2 agonist, des-AA^{1,4,6,11,13}-[DPhe^{2},Aph^{7}(Cbm),DTrp^{8}]-Cbm-SST-Thr-NH$_2$ [39] (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 [37]. 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 [37]. 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 [39] 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 [67], locus coeruleus [18] and periaqueductal gray