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Invited Review

A role for the neuropeptide somatostatin in the neurobiology of behaviors associated with substances abuse and affective disorders

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HIGHLIGHTS

- The somatostatin (SST) system is densely expressed in limbic regions.
- SST plays an important role in modulating emotionality and stress.
- Substances of abuse alter somatostatin system components.
- The SST system may be an important future target for treatments development.

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ABSTRACT

In recent years, neuropeptides which display potent regulatory control of stress-related behaviors have been extensively demonstrated to play a critical role in regulating behaviors associated with substance abuse and affective disorders. Somatostatin (SST) is one neuropeptide known to significantly contribute to emotionality and stress behaviors. However, the role of SST in regulating behavior has received relatively little attention relative to other stress-involved peptides, such as neuropeptide Y or corticotrophin releasing factor. This review characterizes our current understanding of the role of SST and SST-expressing cells in general in modulating several behaviors intrinsically linked to substance abuse and affective disorders, specifically: anxiety and fear; stress and depression; feeding and drinking; and circadian rhythms. We further summarize evidence of a direct role for the SST system, and specifically somatostatin receptors 2 and 4, in substance abuse disorders.

This article is part of the special issue on 'Neuropeptides'.

1. The somatostatin system

Somatostatin (SST) is a cyclic polypeptide first recognized as an inhibitor of growth hormone secretion in 1973 (Brazeau et al., 1973). It was later determined to exist in two distinct biologically active isoforms, SST-14 and SST-28. These isoforms are defined by their N-terminal lengths and result from differential posttranslational processing of the same pro-hormone (Pradayrol et al., 1980). SST has a short half-life of approximately 180 s *in vivo*, being rapidly degraded by endogenous peptidases (Blake et al., 2004). Both isoforms of SST have been shown to inhibit a wide variety of neuro-, gastro-, and immunosignaling molecules throughout the body. SST plays a role in numerous biological functions, such as the regulation of insulin and glucagon levels, gastric secretion, and cell proliferation (Bell et al., 1995; Brown and Taché, 1981; Møller et al., 2003). High SST expression is evolutionarily conserved to occur throughout the rodent and human brain, with particularly dense expression demonstrated in regions involved in cognition, including the cortex and hippocampus; emotional and reward processing, such as the limbic system; and feeding, via the hypothalamus (Bell et al., 1995; Møller et al., 2003; Yamada et al., 1992). Given the wide expression of central nervous system (CNS) SST, it is unsurprising SST has been demonstrated to be involved in numerous additional functions not discussed within this review, such as sleep architecture, nociception, and neuroimmune response, as well as additional neurological disorders, such epilepsy and Alzheimer's disease (Epelbaum et al., 2009; Huang et al., 2018; Møller et al., 2003; Schwartz et al., 1996; Steiger, 2007). This review will focus on the role of SST as a neuromodulator within the CNS, specifically in mediating several behaviors related to drug taking/abuse.

SST is produced in gamma-Aminobutyric acid (GABA)-ergic cells throughout the CNS and released in a calcium-dependent manner (Fontana et al., 2002; Mathé et al., 1993). SST has been most

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extensively studied within the neocortex and hippocampus, where SST expressing (SST+) GABAergic interneurons represent approximately 30% of the total interneuron population (Kubota et al., 2011). This SST + population expresses high levels of spontaneous activity both *in vivo* and *in vitro*, which has been shown to primarily result from intrinsic membrane properties as opposed to synaptic input from other cells populations, and release SST under tonic conditions (Dao et al., 2019; Urban-Ciecko and Barth, 2016). SST + interneurons possess highly diverse anatomical and electrophysiological features [for full review see Markram et al., 2004; Urban-Ciecko and Barth, 2016]. For instance, a large proportion of SST + interneurons are Martinotti cells, which synapse onto the apical dendrites of glutamatergic pyramidal cells and are recruited in a feed-forward manner to inhibit excitability; however, SST has also been found in a sub-population of non-Martinotti interneurons which serve to indirectly excite local pyramidal cells through inhibition of other interneuron populations (Jiang et al., 2019). SST is frequently co-expressed with other neuropeptides in a region and cell-type specific manner. For instance, in the striatum medium sized aspiny SST + neurons most frequently co-express neuropeptide Y (NPY), while in interneuron and GABAergic projecting cells of the central amygdala (CeA) SST + cells most often co-express corticotrophin releasing factor (CRF) (Kovner et al., 2019; Vincent and Johansson, 1983). To what extent these distinct SST + populations are engaged in specific behaviors has yet to be elucidated, but this diversity suggests SST + cells may play a potent role in choreographing neural signaling via both direct and indirect mechanisms.

The two SST isoforms act through binding with five distinct G-protein coupled receptors, somatostatin receptors 1–5 (SSTR1-5), which are expressed at region-dependent levels throughout the brain (Hannon et al., 2002; Viollet et al., 2008). Activation of all 5 receptor subtypes result in the inhibition of adenylyl cyclase (AC) (thus inhibiting cyclic adenosine monophosphate (cAMP) production and protein kinase A (PKA) activity) and the modulation of mitogen-activated protein kinase (MAPK) via the G_i or G_o coupled family of G-coupled proteins (Patel, 1999). The specific contribution of each receptor type in synaptic signaling is only beginning to be fully elucidated, however as SSTR3 mRNA is preferentially expressed in the cerebellum (Kong et al., 1994) and SSTR5 is expressed at negligible levels in the human brain (Thoss et al., 1996) (suggesting a likely lack of translational relevance for SSTR5 targeted therapies), this review will focus on the roles of SSTR1, 2, and 4 [for review on receptor distribution see Selmer et al., 2000].

SST possesses the lowest binding affinity for SSTR1, which has been demonstrated to act primarily as an autoreceptor for SST. This role has been directly demonstrated in the hypothalamus, basal ganglia, hippocampus, and retina, but likely hold true in other SSTR1 expressing regions throughout the brain as well (De Bundel et al., 2010; Leroux et al., 1997; Thermos et al., 2006). SSTR2 has been shown through *in situ* hybridization and immunohistochemistry to be the most highly expressed SSTR in the CNS and is therefore thought to serve as the primary site of SST activity in the brain (Selmer et al., 2000). SSTR2 exists in two spliced variants, SSTR2A and SST2B, which demonstrate an equally high binding affinity for SST (Patel, 1999; Vanetti et al., 1992). These receptors have been demonstrated to be expressed both postsynaptically and presynaptically. It is not yet fully understood how receptor signaling pathways may differ between brain regions and cell types. In the hippocampus, postsynaptic SSTR2 activation reduces cell excitability via membrane hyperpolarization following activation of inwardly rectifying K+ conductance channels, while in the lateral amygdala presynaptically expressed SSTR2 acts to inhibit Ca2+ entry and vesicle exocytosis (Boehm and Betz, 1997; Meis et al., 2005). SST4R binds SST with high affinity and is widely expressed throughout the rodent and human brain, with highest mRNA levels detected in the hippocampus, cortex, amygdala, and hypothalamus (Rohrer et al., 1993; Selmer et al., 2000). In the adult rat forebrain, SSTR4 is predominantly expressed postsynaptically in the distal portion of apical dendrites (Schreff et al., 2000). Additionally, SSTR1, 2, and 4 receptors have been found to be expressed on rodent and human astrocytes (Grimaldi et al., 1997). The specific functional role of each receptor subtype in astrocyte activity has yet to elucidated, however recent work has demonstrated a role of SST in regulating astrocyte Ca2+ signaling and modulation of neuronal signaling. Specifically, within the hippocampus activation of SST + cells induce robust $GABA_B$ receptor-mediated Ca2+ elevations in astrocytes, an effect not observed following activation of parvalbumin (PV+) containing interneurons (Matos et al., 2018). This in turn results in a specific enhancement of SST + interneuron signaling onto neighboring pyramidal cells. Whether this interaction occurs in other SST rich areas will be important in determining the full importance of SST throughout the brain in modulating the tripartite synapse, the synaptic model in which the glial sheath surrounding a synapse is able to respond to and actively modulate ongoing signaling between the pre- and postsynaptic cell (Araque et al., 1999).

The SST system is further widely recognized to play a role in neural plasticity in a brain region specific manner. For instance, exogenous SST application enhances long-term potentiation (LTP) at the mossy fiber-CA3 pyramidal cell pathway of the hippocampus, and SST knockout or pharmacological ablation reduces LTP magnitude at hippocampal Schaffer collateral-CA1 pyramidal cell synapses (Matsuoka et al., 1991). In contrast, exogenous SST application reduces LTP magnitude in the subiculum (Hu et al., 2017). As multiple reviews have been written detailing SST involvement in plasticity in distinct brain regions in recent years, we will not address this subject in depth here. However, SST's role as a modulator of synaptic plasticity is doubtless an important mechanism through which SST contributes to behaviors associated with substance abuse disorders we discuss below (Liguz-Lecznar et al., 2016; Scheyltjens and Arckens, 2016).

2. Anxiety and fear

A high co-morbidity between substance use disorders and anxiety and fear related disorders (such as generalized anxiety disorder and post-traumatic stress disorder (PTSD)) has been extensively demonstrated. The full relationship between impairments/alterations in anxiety and fear behaviors and underlying circuitry in substance abuse disorders has been explored in detail in several recent reviews (Agoglia and Herman, 2018; Centanni et al., 2019; Gimeno et al., 2017; Pleil and Skelly, 2018). In brief summary, neural circuits known to be critically involved in fear and anxiety behaviors are well known to significantly contribute to the initiation of drug use behavior, the development of dependence, and the propensity to relapse to drug use during abstinence.

SST signaling is significantly involved in the behavioral processing of anxiogenic stimuli [Table 1]. Of great interest, a long-acting analogue of SST has previously been found effective in treatment of panic-like attacks in a small sampling of human subjects, suggesting the SST system may be an important target for future treatment development (Abelson et al., 1990). Intracerebroventricular (ICV) SST administration reduces anxiety-like behavior, as well as hippocampal theta rhythm in urethane-anesthetized rats, an effect common to all classes of anxiolytic drugs (McNaughton et al., 2007). Consistently, SST knockout mice display increased anxiety-like behavior under baseline and chronic stress conditions (Lin and Sibille, 2015). However, acute versus chronic inhibition of SST + cell activity in the frontal cortex has been shown to be anxiogenic and anxiolytic, respectively, suggesting inhibition of the SST + interneuron as a whole may induce distinct long-term effects on anxiety-like behavior than knockout of SST alone (Soumier and Sibille, 2014). The SST + GABAergic population in the CeA and BNST are likewise involved in anxiety-like behavior. Increased activity of BNST SST + cells induced a corresponding increase in anxiety-like behavior as measured in the elevated plus maze (EPM) and the open field test (Ahrens et al., 2018). Interestingly, the increase in BNST SST + activity observed in this study was mediated by an increase in CeA SST + cell

Table 1
SOMATOSTATIN AND ANXIETY-LIKE BEHAVIOR. Important abbreviations: BNST: bed nucleus of the stria terminalis; CeA: central amygdala; FC: frontal cortex; ICV: intracerebroventricular; KO: knockout; PL: prelimbic cortex.

System Component	Manipulation	Effect	Reference
SST	ICV SST	↓ Anxiety-like behavior ↓ hippocampal theta activity	Engin and Treit (2009)
SST	Enhanced SST + cell excitability	↓ Anxiety-like behavior	Fuchs et al. (2017)
SST	Chemogenetic inhibition of PL SST + cells	↓ Anxiety-like behavior	Hou et al. (2018)
SST	Knockout	↑ Anxiety-like behavior	Lin and Sibille (2015)
SST	Acute chemogenetic inhibition of SST + cells in FC	↑ Emotionality	Soumier and Sibille (2014)
SST	Chronic chemogenetic inhibition of SST + cells in FC	↓ Emotionality	Soumier and Sibille (2014)
SST	SST + cell ablation in FC	↓ Emotionality at baseline and post-stress	Soumier and Sibille (2014)
SST	SST microinjection	↓ Anxiety-like behavior	Yeung and Treit (2012)
SST	Increased CeA SST + cell excitation	↓ Inhibition on downstream BNST SST + cells ↑ anxiety-like behavior	Ahrens et al. (2018)
SSTR1-5	ICV Receptor Agonists	↓ Anxiety-like behavior with SSTR2 agonist ↔ anxiety-like behavior with SSTR1,3–5 agonists	Engin et al. (2008)
SSTR2	Knockout	↑ Anxiety-like behavior	Viollet et al. (2000)
SSTR2	SST and SSTR2 antagonist	SST anxiolytic effects blocked by antagonist co-injection	Yeung and Treit (2012)
SSTR2 SSTR4	Intra-hippocampal injection	↓ Anxiety-like behavior by SSTR2 agonist; ↔ SSTR4 agonist	Prévôt et al. (2017)
SSTR2 SSTR4	Knockout	↑ Corticosterone levels and anxiety-like behavior in SSTR2 KO ↔ in SSTR4 KO	Prévôt et al. (2017)
SSTR4	Knockout	↑ Anxiety-like behavior	Scheich et al. (2016)
SSTR4	Agonist	↓ Anxiety-like behavior	Scheich et al. (2016)

activity, suggesting an important relationship between SST + cell signaling in distinct regions of the extended amygdala in regulation of anxiety-like behavior.

In keeping with its dense distribution throughout limbic regions, SSTR2 is proposed to serve as the primary receptor mediating SST-induced changes in anxiety-like behavior (Holloway et al., 1996). ICV, intra-amygdala, or intra-hippocampal injection of a SSTR2 agonist, but not a SSTR1 or SST3-5 agonist, reduces anxiety-like behavior in the EPM (Prévôt et al., 2017; Yeung and Treit, 2012). SSTR2 knock out is anxiogenic, while microinjection of a SSTR2 antagonist into the CeA or septum ablates the anxiolytic effects of an SST injection (Engin and Treit, 2009; Viollet et al., 2000; Yeung and Treit, 2012). Indeed, the reduction in anxiety-like behavior induced by SSTR2 agonist treatment in the EPM is equivalent to that produced by the anxiolytic drug diazepam (Engin and Treit, 2009). As the competitive $GABA_A$ receptor antagonist bicuculline has further been shown to reverse the anxiolytic effects of intra-hippocampal SST infusion, SSTR2 induced alterations in GABAergic activity likely mediate this behavior (Engin et al., 2008). However, SSTR4 knockout mice display some increases in anxiety-like behavior in the EPM, suggesting the role of this receptor requires further evaluation and may influence anxiety related behavior in a region-dependent manner (Scheich et al., 2016).

Acute stress is well-known to induce alteration in anxiety-like behavior. SST + cells in the basolateral nucleus of the amygdala (BLA) are activated following EPM exposure, but show decreased c-Fos expression following exposure to predator odor (Butler et al., 2012). This selective activation is proposed to indicate the BLA SST + population plays a specific role in behavior related stress associated with exposure to a novel environment. Interestingly, SST + cell activity in the CeA was likewise found to decrease following predator odor exposure in this study (Butler et al., 2012). The decreased activity in CeA SST + cells may be due to the suggested selectively role of CeA SST + cells in mediating passive versus active strategies when adapting to stressful stimuli. Specifically, optogenetic inhibition of CeA SST + cell signaling promotes active responding to anxiogenic stimuli, such as darting or avoidance, while activation of this population is associated with promotion of passive adaptive strategies, such as freezing (Yu et al., 2016).

This proposed selective involvement of CeA SST + cell activity in passive responding is further relevant to the role of SST in regulating fear behavior in the well-validated fear conditioning model [Table 2]. When an auditory cue is used as a conditioned stimulus, PV + interneurons in the BLA are recruited to inhibit SST + interneurons, resulting in a net increase in glutamatergic signaling (Wolff et al., 2014). A subsection of these BLA glutamatergic efferents which synapse onto SST + cells in the lateral division of the CeA (CeL) are potentiated during fear conditioning, promoting freezing behavior during re-exposure to the stimulus (Li et al., 2013). Interestingly, administration of an SSTR2 agonist into the amygdala was found to strongly attenuate fear expression without impacting initial fear acquisition; though, notably, the agonist was injected in both the BLA and CeA during this study, suggesting further evaluation of the specific role of SSTR2 in fear conditioning within distinct nuclei is needed (Badia-Elder et al., 2001; Kahl and Fendt, 2014). Still, this work suggests interrogation of the precise roles played in fear behavior by distinct signaling molecules released from amygdalar SST + cells is an important area of future research.

Relatively less work has assessed the role of SST cells in the cortex and hippocampal in fear conditioning. SST + interneurons in the medial prefrontal cortex (mPFC) have recently been found to play a critical role in the encoding and expression of cue conditioning fear memory. Specifically, cue fear learning increases excitatory transmission onto mPFC SST+, but not PV+, cells (Cummings and Clem, 2020). These SST + cells displayed increased activity *in vivo* during cue exposure; further *in vivo* excitation or inhibition of this population resulted in a respective increase or decrease in freezing behavior during cue exposure (Cummings and Clem, 2020). Interestingly, this study observed mPFC SST + cells received afferent input from BLA projections, their increased activity following fear conditioning induced increased BLA c-Fos expression, and their modulation of fear behavior depended, at least in part, on BLA activity, suggesting this population may be an important mediator of communication between the mPFC and amygdala during fear conditioning (Cummings and Clem, 2020). The specific role of SST itself relative to GABA released from these interneurons has yet to be evaluated. In contrast, the specific role of hippocampal SST during fear conditioning has received some attention. One study observed global SST knockout significantly reduced hippocampal-dependent context cue fear acquisition without impacting the amygdala-dependent auditory cue fear conditioning (Kluge et al., 2008). The SST knockout was further associated with a decrease in hippocampal plasticity (Kluge et al., 2008). That SST + neurons in CeL have since been found to be required for both the formation and expression of cue-evoked fear memory may suggest a differential impact of acute inhibition of SST + activity compared to SST long-term ablation or distinct roles of SST and other signaling molecules released

Table 2
SOMATOSTATIN AND FEAR CONDITIONING. Important abbreviations: BLA: basolateral amygdala; CeA: central amygdala.

System Component	Manipulation	Effect	Reference
SST	Knockout	↓ Contextual fear conditioning ↔ Auditory fear conditioning	Kluge et al. (2008)
SST	Impair potentiation of BLA→CeA SST + cell input	↓ Fear memory formation	Li et al. (2013)
SST	Optogenetic activation of CeA SST + cells	↑ fear response	Li et al. (2013)
SST	Optogenetic activation of CeA SST + cells	↓ active defensive behavior ↑ passive defensive behavior	Yu et al. (2016)
SST	Optogenetic inhibition of CeA SST + cells	↑ active defensive behavior	Yu et al. (2016)
SST	Fear Learning Prefrontal SST + cell activity	Fear learning ↑ Prefrontal SST + cell activity SST + activity controls fear memory encoding/expression	Cummings and Clem (2020)
SSTR2	Intra-amgdalar agonist during fear acquisition/expression	↔ Fear acquisition ↓ fear expression	Kahl and Fendt (2014)

Table 3
SOMATOSTATIN AND STRESS. Important abbreviations: ACC: anterior cingulate cortex; ACTH: adrenocorticotropic hormone; BDNF: brain-derived neurotrophic factor; BLA: basolateral amygdala; CeA: central amygdala; HPA: hypothalamic-pituitary-adrenal; MeA: medial amygdala.

System Component	Manipulation	Effect	Reference
Plasma SST and Brain SSTR2 Binding	Chronic Mild Stress	↑ Plasma SST ↓ SST2R	Faron-Górecka et al. (2016)
SST	Acute stress or dexamethasone treatment in hippocampal hilar region	↑ SST release	Arancibia et al. (2001)
SST	Acute stress	↑ SST	Brodin et al. (1994)
SST	Acute stress: EPM exposure	↑ SST in BLA; ↔ in CeA ↑ SST in MeA	Butler et al. (2012)
SST	Acute stress: Predator odor	↓ SST in BLA ↓ SST in CeA ↑ SST in MeA	Butler et al. (2012)
SST	Chronic Mild Stress	↓ SST + cells in dorsal and ventral hippocampus	Czéh et al. (2015)
SST	Knockout	↑ plasma corticosterone ↓ BDNF	Lin and Sibille (2015)
SST	Unpredictable Chronic Mild Stress	↓ Cortical SST	Lin and Sibille (2015)
SST and receptors	Acute Predator Exposure	↑ SSTR2 in amygdala and ACC ↔ SST or SSTR1,3-5	Nanda et al. (2008)
SST and receptors	Intra-hippocampal injection	SST analog, SSTR2 and SSTR4 agonist ↓ HPA axis activation SSTR1 or SSTR3 agonist ↔ HPA axis activation	Prévôt et al. (2017)
SSTR2	Knockout and Unpredictable Chronic Mild Stress	↑ Stress sensitivity	Prévôt et al. (2018)
SSTR2	Knockout and stress	↓ Locomotion and exploratory behavior ↑ release of pituitary ACTH	Viollet et al. (2000)
SSTR4	Knockout and Chronic Variable Stress	↑ HPA axis activation following stress	Scheich et al. (2017)
SSTR4	Knockout and Chronic Variable Stress	↑ Stress-induced increase in amygdala FosB	Scheich et al. (2017)

from SST + cells in this behavior (Li et al., 2013). Interestingly, a novel SST + projection from the cortex to the BLA has recently been found to regulate amygdala spike timing during sound-driven aversive/fear behavior, such as that displayed in cue-evoked fear conditioning (Bertero et al., 2019). This may suggest SST + populations throughout multiple brain regions are critical in the acquisition and expression of fear conditioned behavior.

3. Stress response and depression

Similar to fear and anxiety, stress and depressive-associated behaviors have been extensively demonstrated to be both comorbid and interact with substance use disorders (Boden and Fergusson, 2011; Centanni et al., 2019; Davis et al., 2008; Flensborg-Madsen, 2011). Research increasingly supports an important role for SST in modulating CRF-mediated stress response in the CNS [for review, see Stengel and Taché, 2017]. In rodents, SST knockout or SST heterozygous animals show increased basal corticosterone (CORT) levels and reduced brain derived neurotrophic factor (BDNF) and glutamate decarboxylase-67 (GAD-67) levels, while ICV SST administration blocks acute stressor-induced increases in plasma adrenocorticotropic hormone (ACTH), epinephrine, and norepinephrine (Lin and Sibille, 2015; Prévôt et al., 2017). Deletion of GAD67, the synthetic enzyme for GABA, from SST + GABAergic cells was found to not impact hypothalamic-pituitary-adrenal (HPA) axis reactivity, suggesting a critical role for SST itself in modulating this process (Miyata et al., 2019). In human subjects, cerebrospinal fluid SST levels were found to negatively correlate with urinary cortisol levels (Molchan et al., 1993). Following acute stress, SST release is increased in the limbic system, including the amygdala and hippocampus (Arancibia et al., 2001; Brodin et al., 1994). Similar to its role in fear and anxiety, regulation of the stress response is thought to occur primarily through activation of SSTR2 (however, administration of an SSTR3 agonist has also been reported to reduce depressive-like behavior in the forced swim test (FST), suggesting further investigation to the role of this receptor in mediating depressive behavior is needed (Engin and Treit, 2009)). SSTR2, but not SSTR4, knockout mice display increases in CORT and ACTH levels similar to that seen in total knockout of SST itself, with these elevations persisting throughout the lifespan; these mice further show an elevated CORT response to an unpredictable chronic mild stress (UCMS) exposure relative to SST+/+ animals (Prévôt et al., 2018, 2017; Viollet et al., 2000). Predator exposure selectively increased SSTR2 expression in the amygdala and anterior cingulate cortex, but not in the medial habenula (MHb) nor the paraventricular nucleus of the hypothalamus (PVN) (Nanda et al., 2008). However, intra-hippocampal administration of both SSTR2 and 4 agonists (but not SSTR1 or SSTR3) induced a long-lasting inhibition of the HPA axis, suggesting both receptors may contribute to the modulating actions of SST on stress (Prévôt et al.,

Table 4
SOMATOSTATIN AND DEPRESSION. Important abbreviations: CSF: cerebrospinal fluid; ICV: intracerebroventricular; MDD: major depressive disorder.

System Component	Manipulation	Effect	Reference
CSF SST	N/A	↓ SST in CSF of patients during depressive episode	Ågren and Lundqvist (1984)
CSF SST	N/A	↓ SST in CSF of depressive patients	Gerner and Yamada (1982)
CSF SST	N/A	↓ SST in CSF of MDD or Alzheimer's disease	Molchan et al. (1991)
CSF SST	N/A	↓ SST in CSF of MDD or Alzheimer's disease	Molchan et al. (1993)
SST	ICV SST	↓ Depressive-like behavior ↓ hippocampal theta activity	Engin and Treit (2009)
SST	Enhanced SST + cell excitability	↓ Depressive-like behavior	Fuchs et al. (2017)
SST	N/A	↓ SST in amygdala of post-mortem female MDD patients	Guilloux et al. (2012)
SST	Knockout	↑ Depressive-like behavior	Lin and Sibille (2015)
SST	N/A	↓ SST in post-mortem dorsolateral prefrontal cortex of MDD patients	Sibille et al. (2011)
SST	N/A	↓ SST in post-mortem dorsolateral cingulate cortex of MDD patients	Tripp et al. (2011)
SSTR1-5	ICV Receptor Agonists	↓ Depressive-like behavior with SSTR2 and SSTR3 agonists ↔ depressive-like behavior with SSTR1,4,5 agonists	Engin et al. (2008)
SSTR2 and SSTR4	Intra-hippocampal injection	↓ Depressive-like behavior by SSTR2 and SSTR4 agonist	Prévôt et al. (2017)
SSTR2 and SSTR4	Knockout	↑ Depressive-like behavior	Prévôt et al. (2017)
SSTR4	Knockout	↑ Depressive-like behavior	Scheich et al. (2016)
SSTR4	Agonist	↓ Depressive-like behavior	Scheich et al. (2016)
SSTR4	Knockout and Chronic Variable Stress	↑ Depressive-like behavior following stress	Scheich et al. (2017)

2017; Scheich et al., 2016). In addition to acute stress effects, a key factor in the role of SST in stress and depressive behaviors is thought to be the SST system's robust responsiveness and vulnerability to the effects of chronic stress. Chronic stress was shown to reduce SST + cells in the hippocampus by 15–25% (Czéh et al., 2015) and, as mentioned above, SSTR2 knockout potentiates the UCMS-induced elevations in CORT levels (Prévôt et al., 2018). Plasma SST and SSTR2 binding in the BLA, nucleus accumbens (NAc), MHb, and lateral septum were notably decreased following chronic unpredictable stress (Faron-Górecka et al., 2016). This vulnerability suggests an important role of SST in mediating system resiliency to stress-inducing stimuli [Table 3].

A rich literature linking CNS SST signaling and major depressive disorder (MDD) exists [for review see Fee et al., 2017] [Table 4]. In humans, reduced SST expression has been found in the cerebrospinal fluid, anterior cingulate cortex, dorsolateral prefrontal cortex, and amygdala of MDD patients (Ågren and Lundqvist, 1984; Gerner and Yamada, 1982; Guilloux et al., 2012; Molchan et al., 1991; Sibille et al., 2011; Tripp et al., 2011). ICV SST administration or increased SST + cell excitability reduces immobility in the FST, a rodent behavioral model commonly used to assess the efficacy of antidepressant pharmacotherapies (Fuchs et al., 2017; Scheich et al., 2016; Yankelevitch-Yahav et al., 2015). Interestingly, chronic treatment with the tricyclic antidepressant desipramine potentiates the release of NAc dopamine induced by exogenous SST infusion, suggesting a potential role for the SST system in the efficacy of this treatment (Pallis et al., 2001). SST has further been proposed to play a role in the action of another tricyclic antidepressant, imipramine, as response to imipramine treatment was found to correspond with an increase of SSTR2 and SSTR4 mRNA in the MHb (Faron-Górecka et al., 2018). In keeping with this effect, the vast majority of studies support SSTR2 and 4 as the primary mediators of SSTs role in depressive behaviors. SSTR4 knockout animals display increased immobility in the FST, while both SSTR2 and SSTR4 knockout animals display higher susceptibility to stress-induced alterations in behavior, and agonists of both receptors induce decreased immobility in the tail suspension test (TST) (Prévôt et al., 2018; Scheich et al., 2017, 2016). SSTR4 agonist administration further enhanced TST-induced c-Fos expression in several areas associated with emotionality, such as the dorsal raphe nucleus (DRN), amygdala, and bed nucleus of the stria terminalis (BNST) (Scheich et al., 2016). Notably, this agonist-induced increase in TST-induced c-Fos was not detected in the PVN, a finding the authors interpret as the role of SSTR4 in depressive-like behavior occurring outside of the HPA axis (Scheich et al., 2016). This proposal would be consistent with the observed lack of alteration in PVN SSTR2 mRNA expression following stress exposure (Nanda et al., 2008).

Recent work suggests SSTR2 and SSTR4 may mediate distinct aspects of depressive behavior. In the FST, it was observed an SSTR2 agonist reduced immobility time by a selective increase in swimming behavior, while an SST4R agonist reduced immobility via an increase in climbing behavior without impacting overall swim time (Prévôt et al., 2017). In further support of this observation, SSTR2 knockout mice displayed increased immobility due to decreased swimming, while SST4R knockout mice displayed decreased climbing behavior (Prévôt et al., 2017). This is of note as antidepressant alterations of these behaviors are thought to be mediated by distinct neurosignaling mechanisms, with increased swimming mediated by serotonergic activity and increased climbing by noradrenergic activity (Detke et al., 1995; Prévôt et al., 2017). While the specific role of distinct SSTRs in modulating monoamine release has yet to be evaluated, these findings suggests SSTR2 and 4 expressed on distinct neural populations modulate aspects of depressive behavior.

4. Feeding and drinking

Numerous neuromodulators involved in drug abuse likewise mediate the seeking and intake of natural rewards, food, and water. Unsurprisingly, the primary locus of SST modulation of food/water intake is thought to be the hypothalamic nuclei, which expresses high levels of SSTRs [for review see Stengel and Taché, 2019] [Table 5]. SSTR2 agonists increase and SSTR2 antagonists decrease food intake during both the dark and light period of the rodent circadian cycle (Stengel et al., 2010). Notably, this SSTR2 agonist stimulated intake occurred for both normal rodent chow and high fat diets (Stengel et al., 2010). In contrast, ICV SSTR1 and SSTR4 agonists did not alter food intake in the above study. SSTR2 agonist stimulation has also been shown to increase water intake in a manner not dependent on increased thirst resulting from increased chow intake (Stengel et al., 2015). SST has further been proposed to play an extra-hypothalamic role in modulating the relative appetitive value of consumed substances. In a study which allowed simultaneous access to five different liquid solutions, intraperitoneal (IP) injection of SST selectively decreased salt and sucrose intake, but increased ingestion of quinine and hydrochloric acid containing solutions without altering water or total fluid intake (Scalera and Tarozzi, 1998). Given the injection was not CNS specific, it is difficult to rule out influences of peripheral SSTRs in the gastrointestinal tract or tongue on these results; however, they may suggest an overall role of SST in modulating the relative value (both appetitive and aversive) of consumed substances. This role is further supported by recent work in the CeA. Activation of SST + CeA projection neurons were found to drive appetitive behaviors (Kim et al., 2017). This cell

Table 5
SOMATOSTATIN AND FEEDING AND CIRCADIAN RHYTHMS. Important abbreviations: CeA: central amygdala; ICV: intracerebroventricular; IP: intraperitoneal; SCN: suprachiasmatic nucleus; VTA: ventral tegmental areal.

Behavior	System Component	Manipulation	Effect	Reference
Feeding	SST	Optogenetic activation of CeA SST + cells	↑ appetitive behavior ↔ defensive behavior	Kim et al. (2017)
Feeding	SST	IP injection	↑ quinine-HCl and HCL intake ↓ sucrose and NaCl intake ↔ water intake	Scalera and Tarozzi (1998)
Feeding	SSTR1,2,4	ICV Agonist	SST2R ↑ basal or hi-fat diet light-period food intake SSTR1 and SSTR4 ↔ in intake	Stengel et al. (2010)
Circadian Rhythms	SST	SST + cells in basal forebrain activity	Cell lesion ↑ waking in early activity period	Anaclet et al. (2018)
Circadian Rhythms	SST	N/A	↑ SST in SCN of aged rats	Biemans et al. (2002)
Circadian Rhythms	SST	SST depletion with cysteamine	↓ SCN SST Phase advanced free-running rhythm Phase advance in SCN slice firing rate	Fukuhara et al. (1994)
Circadian Rhythms	SST	N/A	SCN SST displays distinct circadian rhythm	Fukuhara et al. (1993)
Circadian Rhythms	SST	SST infusion	Induces time dependent phase delays/advances	Hamada et al. (1993)
Circadian Rhythms	SST	N/A	SCN SST displays distinct circadian rhythm	Shinohara et al. (1991)
Circadian Rhythms	SST	N/A	SCN SST mRNA displays distinct circadian rhythm	Takeuchi et al. (1992)
Circadian Rhythms	SST	SST + cells in basal forebrain activity	↑ SST + cell activity promotes non-REM sleep	Xu et al. (2015)
Circadian Rhythms	SST	Chemogenetic activation of VTA SST + cells	↑ Non-REM sleep	Yu et al. (2019)

population was further found to be activated by water and food exposure as measured by c-Fos expression (Kim et al., 2017). Interestingly, an anterior-posterior gradient has been shown in CeA SST expression in rodents and non-human primates (Kovner et al., 2019). As the anterior and posterior amygdala have been shown to differentially contribute to valence coding of positive and negative stimuli, this gradient may suggest a similarly differential role of SST + cells in these processes (Beyeler et al., 2018). While this remains speculation, the precise role of SST in the amygdala and other reward-associated areas in modulating the intake of aversive or appetitive substances is a rich area of future investigation.

5. Circadian rhythms

A reciprocal relationship between circadian rhythms and substance abuse disorders has been well established over several decades of literature. Alterations in circadian cycle, such as those induced by shift work in humans or phase shifting in rodent models, strikingly alters substance of abuse intake; while substance abuse potently alters neural regulation of the circadian cycle [for review see Depoy et al., 2017; Koob and Colrain, 2019; Rosenwasser, 2015]. Though the specific role of SST in substance abuse-induced disruptions of circadian cycles has yet to be fully evaluated, we will briefly summarize SST + cell involvement in the baseline circadian rhythms, with an emphasis on the sleep/wake cycle [see also Reghunandanan and Reghunandanan, 2006] [Table 5].

The suprachiasmatic nucleus (SCN) of the hypothalamus has long been established as the circadian driving oscillator (Gillette and Tischkau, 1999). SST is expressed in a small cell population concentrated in the dorsal medial region of the SCN and displays a clear circadian cycle in levels of mRNA and peptide expression (Takeuchi et al., 1992; Tanaka et al., 1996). Somatostatin mRNA concentrations were found to be highest and lowest at the onset of the subjective day and night, respectively, with this pattern thought to be an intrinsic biological rhythm rather than entrained to the light cycle as it was observed in blinded rats (Takeuchi et al., 1992). SST protein expression followed a similar pattern to mRNA expression, with expression peaking at ~4 h following the onset, and lowest levels observed at ~20 h into the subjective day in both blinded and non-blinded rats (Fukuhara et al., 1993; Shinohara et al., 1991). Further, alterations in SST levels have been shown to induce changes in rodent circadian rhythms. Depletion of SST via I.P administration of cysteamine in rats induced an approximate 1 h phase advance in the free-running locomotor activity (Fukuhara et al., 1994). Further, in this study cysteamine application to *ex vivo* hypothalamic slices induced a phase advance in the circadian firing rate of SCN cells (Fukuhara et al., 1994). In a different *ex vivo* electrophysiology experiment, SST application was observed to induce phase delays or advances in SCN firing, dependent on experimental time of day (Hamada et al., 1993). Interestingly, in contrast to the decrease in expression observed in several other neuropeptides of the SCN, SST expression was found to increase with age in Wistar rats (Biemans et al., 2002). This may suggest a shifting role of SST in regulation of the SCN across the lifespan.

SST in regions of the CNS outside the SCN has recently been proposed to play a role in regulation of circadian rhythms. The basal forebrain (BF) plays an important role in controlling the mammalian circadian clock and possesses a population of SST + GABAergic neurons which have recently received attention for their potential role in sleep regulation (Yamakawa et al., 2016). The precise role of this population is still an area of ongoing evaluation. Optogenetic activation of this BF SST + cell population in mice has been suggested provide inhibition to three other primary types of BF cells (cholinergic, glutamatergic, and PV + GABAergic) to rapidly promote NREM sleep (Xu et al., 2015). In contrast, another group found through chemo- and optogenetic modulation, as well as genetic ablation, of the BF SST + cell population that these cells likely work to fine tune the level of behavioral arousal rather than act as 'NREM sleep promoting' cells (Anaclet et al., 2018). The authors further suggest impairment of this population may contribute to hyperarousal states observed in many anxiety or fear associated clinical disorders (Anaclet et al., 2018). SST + cells located in the VTA is another population recently suggested to contribute to regulation of the sleep cycle. Chemogenetic activation of these cells induced a 3 h bout of NREM sleep in mice (Yu et al., 2019). Ruther research into the role of SST + cells outside of the SCN in regulation of sleep pattern and circadian rhythms in general, and further the impact of substances of abuse on SST + involvement in these, remains a critical area of future research.

6. Substance abuse disorders

A role for SST in mediating the neurobiological impact of drugs of abuse was first suggested nearly three decades ago when acute and chronic ethanol or cocaine exposure was found to alter SST system components in an exposure-period and region-dependent manner (Barrios et al., 1990; Rodriguez-Sanchez and Arilla, 1990) [Table 6]. Despite this, investigation into the precise role of the SST system in substance abuse disorders has gone relatively neglected until recently, likely due to a previous lack of receptor-specific pharmacological

Table 6
SOMATOSTATIN AND SUBSTANCE ABUSE. Important abbreviations: CPP: conditioned place preference; mPFC: medial prefrontal cortex; PL: prelimbic cortex; NAc: nucleus accumbens.

System Component	Manipulation	Effect	Reference
SST	METH exposure	↔ SST + cells in striatum	Zhu et al. (2006)
SST	SST analog and METH exposure	↓ METH-induced nitric oxide production and cell death	Afanador et al. (2013)
SST and receptors	Acute Cocaine	↔ SST ↓ SSTR in hippocampus and olfactory bulb	Rodriguez-Sanchez and Arilla (1990)
SSTR2	Binge Cocaine	↑ SSTR2 in caudate putamen	Yuferov et al. (2003)
SST	5 day Cocaine Exposure	↓ SST production in cultured cells	Aguila-Mansilla et al. (1997)
SST	Chronic Cocaine	↓ NAc SST + cell excitability	Ribeiro et al. (2018)
SST and receptors	Chronic Cocaine	↔ SST ↔ SSTR in hippocampus and olfactory bulb	Rodriguez-Sanchez and Arilla (1990)
SST	Optogenetic activation of NAc SST + cells	↑ Cocaine-induced locomotion and CPP	Ribeiro et al. (2018)
SST and receptors	Acute Ethanol	↑ SSTR ↓ SST in hippocampus	Barrios et al. (1990)
SST and receptors	Acute Ethanol	↔ SSTR or SST in frontoparietal cortex	Barrios et al. (1990)
SST and receptors	Chronic Ethanol	↔ SSTR ↔ SST in hippocampus	Barrios et al. (1990)
SST and receptors	Chronic Ethanol	↓ SSTR ↔ SST in frontoparietal cortex	Barrios et al. (1990)
SST	Chronic Ethanol	Cortical martinotti (SST+) cell excitability ↑ males/↓ females	Hughes et al. (2020)
SST and receptors	Ethanol Withdrawal	↓ SSTR ↔ SST in frontoparietal cortex	Barrios et al. (1990)
SST and receptors	Chronic Ethanol in virgin rats	↔ SST ↓ SSTR	Barrios et al. (2005)
SST and receptors	Chronic Ethanol parturient rats	↑ SST ↓ SSTR	Barrios et al. (2005)
SSTR4	Long-term Modest Ethanol Intake	↓ NAc SSTR4 following 2 or 4 months intake ↔ NAc SSTR4 following 10 months intake	Jonsson et al. (2014)
SST	SST + cell activity in PL	PL SST + cells required for morphine CPP and hyperlocomotion	Jiang et al. (2019)
SST	Chemogenetic inhibition of PL SST + cells	↓ Morphine-induced locomotion and CPP	Hou et al. (2018)
SST cell morphology	Chronic Morphine	↑ total dendrite length and dendritic complexity in mPFC	Wang et al. (2019)
SSTR1-5	Intermittent Heroin	↓ SSTR1 and SSTR3 in CP; ↔ SSTR2,4,5 in CP	Schlussman et al. (2010)

agents. A significant proportion of research has focused on the role of SST in the striatum, an unsurprising focus given the critical role of this region in substance abuse. SST is expressed in striatal medium-sized aspiny neurons which potently modulate behavior (Tepper et al., 2010). For example, exogenous SST infusion increases striatal dopamine release via presynaptic mechanisms and alters locomotion at a level comparable to that induced by amphetamine administration (Hathway et al., 2002). Similar to many other neurosignaling systems, different substances of abuse have been demonstrated to differentially impact SST system expression within the same region. Striatal SST + cells appear to be particularly resilient against methamphetamine-induced apoptosis relative to other cell types, potentially due to a lack of NMDA NR2A/2B receptor expression (Zhu et al., 2006). Further, SST agonist injection attenuated methamphetamine-induced apoptosis (Afanador et al., 2013). Heroin exposure has been found to increase SSTR1 and SSTR3, but not SSTR2 or SSTR4, mRNA are in this region (Schlussman et al., 2010). In contrast, SSTR4 mRNA expression is significantly decreased in the striatum following 10 months of voluntary two-bottle ethanol intake (Jonsson et al., 2014). In regard to cocaine, SST + cell activation potentiates, and inhibition attenuates, the behavioral effects of cocaine in mice (Ribeiro et al., 2018). This study further found cocaine exposure decreased SST + cell intrinsic excitability. One or three days cocaine binge exposure is sufficient to induce a selective increase in caudate putamen SSTR2 expression, without impacting levels of any other SSTR (Yuferov et al., 2003). Interestingly, acute cocaine has recently been found to activate afferent projections onto SST + interneurons in the NAc, suggesting extra-striatal regulation of SST + cell signaling in the NAc may play an important role in mediating striatal signaling in cocaine use and potentially in modulating the acute effects of other substances of abuse (Ribeiro et al., 2019). It is notable that the ventral hippocampus has been demonstrated to directly synapse onto NAc SST + interneurons, suggesting this region may serve as one source of SST + interneuron modulation during drug exposure (Scudder et al., 2018). Together, these data demonstrate SST system components are potently altered during drug exposure, suggesting specific components of this system may serve as viable treatments for specific forms/stages of substance abuse disorders.

While less work has been performed outside of the striatum, the current literature suggests the hippocampus SST system may likewise play a role in the development of drug dependence. Chronic ethanol ingestion reduced SST + cell number in the hippocampus of rodents and chronic cocaine administration reduced SSTR expression in the hippocampus of rats (Barrios et al., 2005; Rodriguez-Sanchez and Arilla, 1990). Interestingly, intra-hippocampal administration of a SSTR4 agonist induced a dose-dependent selective enhancement of cue-based memory formation, leading to the speculation that hippocampal SSTR4 may serve to selectively mediate the switch from hippocampal- to striatal-based learning strategies (Gastambide et al., 2009). Given the transition to more habitual, striatal-based behaviors is a hallmark of drug dependence, this role of hippocampal SSTR4 and drug-induced alterations in its function has notable implications for drug-taking behavior.

Substances of abuse significantly impact the cortical SST system. Chronic ethanol ingestion decreases SSTR immunoreactivity and SST-mediated inhibition of AC activity in the frontoparietal cortex, while a 5-day incubation with cocaine reduced SST expression in cultured fetal rat cortex cells *in vitro* (Aguila-Mansilla et al., 1997; Barrios et al., 2005). Chronic ethanol exposure via daily intragastric gavage has further been found to sex-dependently alter cortical martinotti cell (the predominant SST + cell type in the cortex) function, enhancing excitability in male and reducing excitability in female rats (Hughes et al., 2020). Repeated morphine treatment alters the dendritic morphology of mPFC SST + interneurons, increasing total dendrite length and complexity for at least seven days into withdrawal (Wang et al., 2019). This altered morphology is coupled with an increased intrinsic membrane excitability and an increase in inhibitory transmission onto neighboring PV + interneurons by SST + cells (Jiang et al., 2019). These data suggest a potentially important role of SST + interneurons

in morphine intake, in keeping with the finding that inhibition of mPFC SST+, but not PV+, interneurons significantly decreased morphine behavioral effects and conditioned place preference (Hou et al., 2018). This relationship is thought to be due to the prominent expression of delta opioid receptors on SST + relative to PV + cells (Milner et al., 2013). Given the extensive evidence for a role of the SST system in pain processing [for review see Huang et al., 2018], further evaluation of the role of the SST system in the neural effects of morphine and, further, the impact of alterations in cortical SST + cells on the interaction between pain and other drugs of abuse is an area of great interest.

Differences in innate SST signaling may contribute to differences between mouse genetic strains in the intake of rewarding substances/drugs of abuse. The 129P3/J and C57BL/6J strains of mice are known to display significant baseline differences in preference for sweetener or ethanol containing solutions, anxiety-like behavior, and behavioral response to cocaine and opioids (Bachmanov, 2001; Bachmanov et al., 1996; Cunningham, 2019; Schlussman et al., 2010). While numerous genetic differences likely contribute to these differences, it is notable that the more 'drug sensitive' and ethanol-preferring C57BL/6J strain expresses significantly lower levels of SSTR2 and SSTR4 and higher levels of SST3R in the caudate putamen compared to 129P3/J (Schlussman et al., 2010). This difference in SST4R between strains is of particular interest as the promotor region of SSTR4 is found to be methylated in 21.6% of clinical patients with an alcohol use disorder compared to only 2.3% of control subjects (Berent et al., 2017). While it is difficult to draw direct comparisons based on these data alone, given the role of SSTR4 in depressive-like behaviors discussed above, these results may indicate an important link between SSTR4 function and vulnerability to development of a substance abuse disorder.

7. Conclusions

Overall, this review sought to highlight the SST system, and particularly SSTR2 and SSTR4, as critical future targets for the understanding and treatment of behaviors closely related to and substance abuse disorders themselves. The SST system is expressed throughout the brain and notably involved in modulation of numerous behavioral phenotypes associated with the initiation, escalation, and relapse to drug-taking behavior, including anxiety, depression, stress, and fear behavior. While SSTRs are further involved in general feeding and drinking behavior, in this review we discussed how receptors involved in these processes are predominantly expressed in regions distinct from those involved in reward and emotionality. Further, as overall SST system activation increases food/water intake, yet decreases anxiety- and depressive-like behaviors and the reinforcing effects of drugs of abuse, the same SST system components appear to differentially modulate normal consumption and behaviors underlying substance use disorders. This differential modulation is important in consideration of these SST receptors as potential therapeutic targets for substance abuse disorders, as it may enable the specific targeting of maladaptive behaviors without interrupting general appetitive behavior.

While these data are suggestive of an important role for the SST system in substance abuse disorders, a great amount of work remains to be done in parsing out the precise role of system components within specific brain regions. Differences in relative receptor expression patterns between drug-preferring and non-preferring animals, as well as the specific changes in SST + cell innervation of excitatory or inhibitory cells seen following morphine exposure in the mPFC, indicate relatively small alterations in SST system expression and morphology can have vast effects on local circuitry and behavioral phenotype. This point is further underlined by the potent role striatal SST + cells exert on the behavior effects of cocaine despite representing less than 1% of the NAc cell population. Further, the precise mechanisms through which SST exerts influence within each region, and even onto each individual cell types, on a synaptic level requires further investigation. For instance, SST is able to both enhance and reduce LTP expression within the hippocampus in a synapse-specific manner. Additionally, SST may modulate an individual synapse through binding to pre- or postsynaptic located receptors, or influence the signaling at potentially thousands of synapses by modulating local astrocyte network Ca2+ elevations. Finally, the relative contribution of SST and that of co-expressed signaling molecules, most notably GABA, in behavioral alterations induced by modulating SST + cell activity remains to be thoroughly interrogated. Together, these data demonstrate that while research has come far in the nearly fifty years since the original discovery of SST, a long road remains in elucidating the full functional and therapeutic potential of this system.

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