Reduced brain somatostatin in mood disorders: a common pathophysiological substrate and drug target?

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INTRODUCTION
Mood disturbances are commonly observed in many neurological disorders. The chronic, recurrent and long duration of mood disturbances not only place an enormous emotional and financial burden on patients, but also on their families and society. Nearly 10% of all primary care office visits are depression-related (Stafford et al., 2000), but only 30% of patients with mood disturbances achieve remission with initial treatment (Tirvadi et al., 2006). Somatostatin is a peptide expressed in multiple organs in the body. Somatostatin (also known as somatotrophin release inhibiting factor and often abbreviated as SST, SRIF, or SOM) acts as a modulatory and inhibitory neuropeptide that is co-localized with gamma-aminobutyric acid (GABA), and that is involved in regulating multiple aspects of physiological and behavioral stress responses, including inhibition of hypothalamic hormone release, amygdala central nucleus output, and cortical local circuit integration of sensory input. Research advances over the past three decades suggest a critical role for somatostatin in the pathophysiology of mood disorders, and potential new therapeutic strategies. Several recent reviews have summarized the role of the somatostatin system, including in receptor subtypes (Patel, 1999; Cuaba and Deournaud, 2001), pharmacological developments (Noggers and van der LELY, 2009), and during normal and pathological aging (Patel, 1999; Viollet et al., 2008; Martel et al., 2012).

Our knowledge of the pathophysiology of affect dysregulation has progressively increased, but the pharmacological treatments remain inadequate. Here, we summarize the current literature on deficits in somatostatin, an inhibitory modulatory neuropeptide, in major depression and other neurological disorders that also include mood disturbances. We focus on direct evidence in the human postmortem brain, and review rodent genetic and pharmacological studies probing the role of the somatostatin system in relation to mood. We also briefly go over pharmacological developments targeting the somatostatin system in peripheral organs and discuss the challenges of targeting the brain somatostatin system. Finally, the fact that somatostatin deficits are frequently observed across neurological disorders suggests a selective cellular vulnerability of somatostatin-expressing neurons. Potential cell intrinsic factors mediating those changes are discussed, including nitric oxide induced oxidative stress, mitochondrial dysfunction, high inflammatory response, high demand for neurotrophic environment, and overall aging processes. Together, based on the co-localization of somatostatin with gamma-aminobutyric acid (GABA), its presence in dendritic-targeting GABA neuron subtypes, and its temporal-specific function, we discuss the possibility that deficits in somatostatin play a central role in cortical local inhibitory circuit deficits leading to abnormal corticolimbic network activity and clinical mood symptoms across neurological disorders.

Keywords: somatostatin, somatostatin-expressing interneurons, SST, SOM, SRIF, depression, mood disorders, GABA inhibition
Table 1 | Low somatostatin in human neurological disorders.

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LOW SOMATOSTATIN IN NEUROPSYCHIATRIC AND NEURODEGENERATIVE DISORDERS

MAJOR DEPRESSIVE DISORDER

Patients with major depressive disorder (MDD) show decreased somatostatin levels in the cerebrospinal fluid (CSF; Agren and Lundqvist, 1984, Molchan et al., 1991, Kling et al., 1993), and transiently decreased CSF somatostatin which normalize with recovery in MDD (Rubinow et al., 1985, Post et al., 1988). Evidence for low levels of CSF somatostatin was found to correlate significantly with elevated urinary cortisol in MDD patients (Molchan et al., 1993). This is consistent with the altered hypothalamic-pituitary-adrenal (HPA) axis function described in some depressed patients (Holsboer, 2000). The route and characterization, however, from CSF somatostatin to MDD pathophysiology is not direct, potentially due to a paucity of information on factors regulating CSF somatostatin, and to inconclusive somatostatin/HPA axis studies in MDD patients. Hence, despite these early findings, interest in somatostatin in mood disorders has declined over time.

Human post-mortem studies from our group have described region-specific somatostatin deficits in MDD patients, including a down-regulation of somatostatin gene expression in the dorsolateral prefrontal cortex (dPFC), subgenual anterior cingulate cortex (sgACC), and amygdala (Sibille et al., 2011; Tripp et al., 2011, 2012, Guilloux et al., 2012). In addition, two peptides co-localized with somatostatin, neuropeptide Y and cortistatin, are both significantly down-regulated in MDD patients (Tripp et al., 2011, 2012). These three neuropeptides (somatostatin, neuropeptide Y, and cortistatin) are markers of GABAergic neurons that specifically target the dendritic compartment of pyramidal cells (de Lecua et al., 1997; Viollet et al., 2008), and that are essential in gating incoming sensory information (Figure 1). Other types of GABAergic cell markers, such as parvalbumin and cholecystokinin, are mostly not affected by MDD (although see Tripp et al., 2012). Interestingly, these somatostatin deficits were systematically more robust in female subjects across cohorts and regions (Sibille et al., 2011, Tripp et al., 2011, 2012; Guilloux et al., 2012), consistent with the female heightened vulnerability to develop MDD, and suggesting that low somatostatin may represent a molecular correlate of sexual dimorphism in vulnerability to affect dysregulation. Notably, these findings are also consistent with earlier postmortem studies showing reduced calbindin-positive cell numbers in MDD (Rajkowska et al., 2007, Maciag et al., 2011).
Somatostatin deficits in mood disorders

FIGURE 1 | Schematic of somatostatin signaling, pathological regulators and biological functions relevant to affect regulation. Somatostatin pathway activity is responsive to (left panel), and regulates (right panel), several biological events, and molecular and cellular properties that have been linked to mood disturbances. Somatostatin and somatostatin-expressing interneurons are key conduits for regulating incoming information and pyramidal cell function. In contrast, other GABA neurons subtypes targeting the perisomatic pyramidal cell compartment are mostly not affected in major depression. NPY, neuropeptide Y; PYR, pyramidal neuron; PV, parvalbumin.

2010), as somatostatin is mostly expressed in a subgroup of calbindin-positive cells (reviewed in Viollet et al., 2008). Converging evidence from down-regulation of somatostatin co-localized GABA markers in MDD across multiple human post-mortem studies suggests that this particular GABA subpopulation in the forebrain is selectively vulnerable, among other subtypes of GABA neurons. Furthermore, these local cell circuit-based findings introduce a new role for somatostatin in depression, which is distinct from its previously investigated role in the regulation of the HPA axis (Rubinow et al., 1983; Molchan et al., 1993; Weckbecker et al., 2003).

OTHER NEUROPSYCHIATRIC DISORDERS

Schizophrenia is a neuropsychiatric disorder characterized by positive (e.g., hallucination), negative symptoms (e.g., emotional blunting, apathy) and cognitive symptoms. Somatostatin deficits in schizophrenia are demonstrated by a reduction of CSF somatostatin (Bissette et al., 1986; Rimikizumi et al., 1990), decreased somatostatin gene expression in the dIPFC (Morris et al., 2008; Guillotet-Bongaarts et al., 2013), and decreased number and density of somatostatin-expressing neurons in the hippocampus (Konradi et al., 2011a), caudal entorhinal cortex and parasubiculum (Wang et al., 2011). Changes in somatostatin are also identified in bipolar disorder, which is clinically characterized by fluctuating mood. Studies in subjects with bipolar disorder indicate decreases in somatostatin cellular density in the caudal entorhinal cortex and parasubiculum (Wang et al., 2011), number of somatostatin-expressing neurons in the hippocampus (Konradi et al., 2011b), somatostatin gene expression in the dIPFC (trend level; Sibille et al., 2011) and hippocampus (Konradi et al., 2011b). In addition, patients with bipolar disorder show elevated CSF somatostatin during manic states (Sharma et al., 1995).

NEURODEGENERATIVE DISORDERS

Alzheimer’s disease is a neurodegenerative disease with neuropsychiatric symptoms (Bungener et al., 1996). Decreased CSF somatostatin (Bissette et al., 1986; Tamminga et al., 1987) and decreased somatostatin immune-reactivity across cortical and subcortical regions is reported in subjects with Alzheimer’s disease, including temporal cortex, frontal cortex, and hippocampus (Davies et al., 1980; Morris et al., 2008; Guillozet-Bongaarts et al., 2013; Candy et al., 1983; Dournaud et al., 1994). Depression is a common comorbid symptom in Parkinson’s disease and predicts greater disability at any assessment point (Aarsland et al., 1999). Reduced CSF somatostatin, decreased somatostatin immuno-reactivity, and binding sites are also observed in the temporal cortex and frontal cortex of patients with Parkinson’s disease (Beal et al., 1986; Rossor et al., 1980; Davies and Terry, 1981; Candy et al., 1983; Dournaud et al., 1994). Notably, reduced CSF somatostatin in Parkinson’s disease appears to be irreversibly present at the onset of symptoms (Dupont et al., 1982).

REDUCED SOMATOSTATIN AND LOW MOOD?

The evidence outlined in this review provides only a glimpse of the potential full range of somatostatin deficits across neurological disorders, as multiple other brain regions and disease categories await further characterization (Table 1). Taken together, the cumulative evidence demonstrates that somatostatin deficits are common neurochemical and molecular features in individuals with neurological disorders, regardless of their categorical diagnosis. While somatostatin studies of cell number and gene expression in human...
postmortem brains suggest a specific alteration of somatostatin-positive neurons across neurological disorders, it is possible that changes and dys-synchronization of additional components of local neuronal circuits contribute to a common symptom dimension, which we speculate includes low affect and mood dysregulation. Hence, this review is not comprehensive, but rather, highlights the recent findings in brain somatostatin signaling and the potential role of somatostatin deficits in affect dysregulation for integrating categorical models of mood symptoms into a dimensional model across neurological disorders.

**Somatostatin: Genes, Neurons and Pharmacology**

Somatostatin is a modulatory neuropeptide that synergizes with GABA-mediated inhibition, and that specifically targets the distal dendritic compartment of pyramidal neurons in cortical local circuits (Kawaguchi and Kubota, 1997; Genter et al., 2012). Somatostatin inhibits release of numerous hormones from the hypothalamus, including corticotrophin releasing hormone (CRH; Wang et al., 1987; Patel, 1999). The somatostatin gene product is composed of 14 or 28 amino-acid residues. Both forms of somatostatin, somatostatin-14 and somatostatin-28, are generated by tissue-specific post-translational processing of the 116 amino-acid pre-pro-somatostatin peptide (Warren and Shields, 1984; Tostivint et al., 2008). Somatostatin-14 is predominantly produced in the central nervous system (CNS) but also in many peripheral organs (Epelbaum, 1986). Somatostatin-28 is mainly synthesized along the gastrointestinal tract (Fitz-Patrick and Patel, 1981). The 5′-upstream sequence of the somatostatin gene contains cyclic-AMP response element (CRE; monstrousy et al., 1986), making its expression activity-dependent. Thus, somatostatin expression is preferentially altered by various stressors, such as seizures (Vezzani and Hoyer, 1999; Tallent and Qiu, 2008) and electrical foot shock (Posonar et al., 2010). Moreover, mice with conditional homozygous and constitutive heterozygous brain-derived neurotrophic factor (Bdnf) knockout or disruption of Bdnf transcripts show decreased somatostatin expression in the brain (Guilloux et al., 2012), demonstrating that somatostatin expression depends on Bdnf signaling. However, the molecular mechanisms by which this neurotrophic factor controls somatostatin and somatostatin-expressing neurons are still unknown.

Somatostatin, cortistatin and their receptors are closely intertwined systems (de Lecea et al., 1996, 1997; reviewed in Patel, 1999, Olias et al., 2004). Accordingly, there are currently very few reports linking somatostatin gene polymorphisms with neurological disorders. A primate-specific single nucleotide polymorphism (SNP) in the human somatostatin gene [C/T polymorphism (rs4988514)] is associated with increased risk in Alzheimer’s disease progression and additive effect with the APOE epsilon4 allele (Vepsalainen et al., 2007; Xue et al., 2009), although this was not confirmed in larger genome-wide association studies (GWAS) (Hollingworth et al., 2011; Guerreiro et al., 2013). Leu48Met and Pro335Leu SNPs in the SST5 gene are of potential significance to patients with bipolar disorder (Nygarden et al., 2002), but no associations of SST5 SNPs are found in patients with autism (Lauritsen et al., 2003). The paucity of associations with somatostatin gene variants is surprising and may reflect either strong negative selection against genetic variations in this gene, or alternatively, dilution of signal due to heterogeneity of DSM-IV-based cohorts in genetic association studies. So, dimensional phenotypes, as defined by clusters of mood symptoms, which are closer to gene functions may have implications for future genetic studies of somatostatin and other genes.

**Somatostatin-Expressing Neurons: Diversity and Roles**

Gamma-aminobutyric acid (GABA) neurons are a diverse group of inhibitory cells which co-release neuropeptides in order to support a fine-tuning of neuronal signaling and architecture. The local inhibitory circuits provide spatiotemporal control of information processing through at least 20 subtypes of cortical GABA neurons, which are based on their expression of different calcium binding proteins and neuropeptides, localization, targeting, and differential electrophysiological properties. Recent detailed reviews on GABA neuron subpopulations have been published (Csaba and "fphar-04-00110" — 2013/9/5 — 15:44 — page 4 — #4)
and visual cortex of mouse (Gonchar et al., 2007; Xu et al., 2010) and somatostatin in the frontal cortex, primary somatosensory cortex and visual cortex of mouse (Gonchar et al., 2007; Xu et al., 2010) and the visual cortex of rat (Gonchar and Burkhelter, 1997).

Recent reports focusing on the patterns of cortical neuronal connectivity show that somatostatin-expressing interneurons mediate the firing of pyramidal neurons with a fine level of specificity among cortical layers. Integrating optogenetic and electrophysiology approaches, mouse somatostatin-expressing interneurons in layer 2/3 of the somatosensory cortex provide a tonic inhibition to the distal dendrites of excitatory pyramidal neurons by sharpening selectivity during periods of quiet wakefulness, which may contribute to synchronized firing in cortical networks and sensorimotor integration (Gentet et al., 2012). Interestingly, in mouse somatosensory cortex, somatostatin-expressing interneurons show a spatially precise connectivity with pyramidal neurons through direct targeting in layers 2/3 or indirectly through inhibition of local parvalbumin interneurons in layer 4 (Xu et al., 2013). Moreover, in layers 2/3 of the mouse prefrontal cortex, somatostatin-expressing interneurons compartmentalizes inhibitions of calcium signaling to spine heads, not shafts, suggesting that dendrite-targeting inhibition through somatostatin-expressing interneurons may contribute to downstream cellular processes such as synaptic plasticity (Chiu et al., 2013). In mouse visual cortex, somatostatin-expressing interneurons are found to mediate response levels of specific subsets of pyramidal neurons whereas parvalbumin-expressing neurons alter response gain (Wilson et al., 2012). Parvalbumin-expressing neurons receive excitatory input from the thalamus and make strong synapses on the soma and axons of their target cells (Kawaguchi and Kubota, 1997) to control spike timing of the output neurons. In contrast, somatostatin-expressing neurons mostly do not receive input from thalamus (Bergie et al., 2003; Cruikshank et al., 2010) and are instead activated through feed-forward mechanisms by activated pyramidal neurons. Somatostatin-expressing interneurons preferentially target distal dendrites of pyramidal neurons in layer 2/3 to modulate the processing of incoming sensory information before it is integrated at the soma level (Di Cristo et al., 2004; Markram et al., 2004; Tan et al., 2008; Murayama et al., 2009; Xu et al., 2013). Hence, the distinct GABAergic and prototypical inhibitory populations, expressing either parvalbumin or somatostatin, shape the spatiotemporal control of multiple post-synaptic potentials in cortical local circuits, and provide a framework to investigate the role of inhibitory circuits in physiology and pathology.

GENETIC APPROACHES TO INVESTIGATE THE SOMATOSTATIN SYSTEM

Mice mutant for somatostatin were created by deleting the coding region of the pre-pro-somatostatin (the last ten codons of the first exon; Zeyda et al., 2001). Somatostatin knockout (KO; SstKO) mice and somatostatin knockout (KO; SstKO) mice show intact motor coordination and motor learning, but have a significant impairment in motor learning as demands of motor coordination are increased. Overall, a detailed analysis demonstrated that Sst−/− mice are healthy, fertile, and show no overt behavioral phenotypes, including anxiety-like behavior in the open-field and fear conditioning tests. Notably, Sst−/− mice display high basal plasma levels of corticosterone and growth hormone (Zeyda et al., 2001), confirming a somatostatin-mediated inhibition of HPA axis function. Similarly, mice lacking individual Sst1,3 receptors have been tested in numerous biological fields. Of these, Sst3, emerged as the primary receptor of interest (Zeyda and Hochgeschwender, 2008), and Sst3−/− mice display increased anxiety-like behavior in the elevated plus maze and open field, increased immobility in the forced swim test, decreased locomotion coupled with an increase of pituitary adrenocorticotropic hormone release instead of growth hormone (Viollet et al., 2008). In line with the observed changes in Sst3−/− mice, acute predator stress in rats led to up-regulated Sst2 gene expression in the amygdala and cingulate cortex, shown correlated with Fos expression in the amygdala (Nanda et al., 2008). As the product of a different gene, cortistatin shares a high structural and functional similarity with somatostatin-14 (de Lecea et al., 1996, 1997). Notably, compared with the weak inhibitory effects of somatostatin on the basal release of CRH from rat hypothalamus and hippocampus, cortistatin exhibits strong inhibition of the expression and release of basal CRH (Tringali et al., 2012). These findings suggest that Sst2 may regulate affective phenotypes and HPA axis responses both through somatostatin and cortistatin. Given the limitations of human studies, Sst−/− mice provide an opportunity to explore the causal role of somatostatin in affect dysregulation and the underlying neural mechanisms. Such insights, however, will require systematic behavioral characterization with fine spatial and temporal resolution by including female cohorts and region-specific manipulation at different developmental stages. Based on the published studies to date, it is still unclear whether these mutants recapitulate behavioral features of mood disorders. Knowing the effects of somatostatin signaling on neuroendocrine regulation, future studies need to assess the molecular and cellular systems that somatostatin mutations converge upon, and where the exact neural circuits are affected. Moreover, combining genetic and environmental factors in animal models is critical to enhance the accuracy of disease modeling and translational efforts. For example, acute or chronic exposure to stress or to stress hormones may capture how such endogenous factors determine the vulnerability to external insults, in contrast to baseline behavioral testing. In addition, mood disorder-related sex differences are observed in community-based epidemiological studies, where the factor of seeking treatment is removed (Kornstein et al., 2000; Festinger et al., 2008; Leach et al., 2008) and findings of low somatostatin in the amygdala appear more robust in postmortem studies of female MDD subjects (Tripp et al., 2012), suggesting that gender/sex may represent a biological predisposing factor, or at least a moderating factor, in the intrinsic vulnerability of the somatostatin system.

Although many mood disorders emerge during adolescence (Pass et al., 2008), behavioral abnormalities including affect dysregulation are often heritable and apparent before diagnostic criteria are met (McGiffin et al., 2003; Geller et al., 2008). It is unclear when somatostatin deficits occur and potentially begin to contribute to the formation of affective symptoms. Tracking somatostatin system using new anatomic techniques with refined cellular...
As native somatostatin peptides have a very short half-life time (approximately 1–3 min; Shepherd et al., 1979), long-acting and highly potent somatostatin analogues are currently available for the treatment of acromegaly and neuroendocrine tumors, including octreotide (long-acting; LAR-OCT; Bauer et al., 1982) and Lanreotide (slow release or autogel; Reven, 2005; Molitch, 2008). Compared to somatostatin, pharmacological tools of the free somatostatin receptor subtypes have lagged behind, partly due to the lack of high-affinity antagonists.

In addition, several novel somatostatin therapy models are available: (1) Universal somatostatin (Schmid and Schoeffter, 2004): a somatostatin molecular analog with high binding affinity to all or most human somatostatin receptors. An example is SOM230, which interacts with Sst1,2,3 and particularly potent at Sst5, compared with LAR-OCT; (2) Chimeric somatostatin/dopamine molecule (Savaru et al., 2002; Promello et al., 2005): a somatostatin and dopamine hybrid agonist, based on reports that dopamine and somatostatin receptors can heterooligomerize to enhance functional responses (Rochville et al., 2000). An example is BIM-23A760, which accelerates the suppression of growth hormone and adrenocorticotropic hormone by the interaction with Sst5 and Drd2 simultaneously; (3) Chimeric somatostatin vaccinations (Hoffer, 2012): a fusion protein expressing chloramphenicol acetyl transferase protein and somatostatin. Two somatostatin vaccinations, H17 and H18, can effectively reduce weight gain and reduce final body weight percentage of normal, non-obese mice and mice with diet-induced obesity via the intra-peritoneal route; (4) Non-peptide antagonists, such as SRA880 (Sst1 selective), ACQ090 (Sst3 selective) and Sst4 selective potentiating octreotide (long-acting; LAR-OCT; Bauer et al., 1982) and Lanreotide (slow release or autogel; Reven, 2005; Molitch, 2008). An example is BIM-23A760, which accelerates the suppression of growth hormone and adrenocorticotropic hormone by the interaction with Sst5 and Drd2 simultaneously; (3) Chimeric somatostatin vaccinations (Hoffer, 2012): a fusion protein expressing chloramphenicol acetyl transferase protein and somatostatin. Two somatostatin vaccinations, H17 and H18, can effectively reduce weight gain and reduce final body weight percentage of normal, non-obese mice and mice with diet-induced obesity via the intra-peritoneal route; (4) Non-peptide antagonists, such as SRA880 (Sst1 selective), ACQ090 (Sst3 selective) and Sst4 selective β peptide agonists (Rivier et al., 2003; Hoyer et al., 2004). Despite this extensive list, the practical use of somatostatin in the brain is hampered by the multiple effects of the peptide, by the need for small molecules targeting specific, high affinity receptors on the target cells in specific brain regions, and by the need for feasible routes of administration that lead to fast delivery into the brain. The potential for using somatostatin analogues as treatment in the CNS is emerging for treatment of epilepsy (Vezzani and Treit, 2009; Tallent and Qiu, 2008), pain (Mollenholt et al., 1994; Tauras et al., 1994; Tauras et al., 1997; Pallis et al., 2006, 2009). Repeated administration of imipramine, maprotiline, mianserin, carbamazepine or zotepine has no effect on somatostatin levels in several brain regions of rats (Weiss et al., 1987; Kakigi et al., 1992). While some somatostatin receptor seem to exert anxiolytic or antidepressant-like effects, there is no direct evidence supporting somatostatin receptors as downstream targets of current antidepressants. Together, these findings suggest that somatostatin levels are mostly unchanged by antidepressants. It is unclear whether somatostatin, GABA, or GABA functioning in somatostatin-expressing interneurons may be the real mediators or antidepressant targets. Future studies are needed to determine the involvement of somatostatin receptors and associated intracellular signaling pathways in the therapeuti-efects of antidepressants, or whether somatostatin effects are independent of current antidepressant modalities.

**Potential Mechanisms of Selective Vulnerability of Somatostatin-Expressing Interneurons**

It is possible that low somatostatin in diseases acts as a biomarker for deregulated function of somatostatin-expressing neurons. As such, it is essential to identify upstream factors responsible for the dysfunction of somatostatin-expressing interneurons in neurological disorders. We speculate that intrinsic cellular properties in somatostatin-expressing neurons may determine their selective vulnerability to various insults. Pathways underlying this high vulnerability may include high intrinsic oxidative stress related to mitochondria, high sensitivity to inflammation, high dependence on neurotrophic environment, and cellular developmental and aging processes. These canonical pathways might provide novel cell-based perspectives in the treatment of affected somatostatin-expressing cells across neurological disorders. 

**Oxidative Stress and Mitochondrial Dysfunctions**

Oxidative stress produced by mitochondria during respiration is a common pathogenic mechanism implicated in neurological disorders (Sorce and Krause, 2009; Stefanescu and Ciobica, 2012). Depressed states in mood disorders are associated with decreased...
between subjects with MDD and mice with genetically-altered somatostatin deficits. In addition, Bdnf-Tkβ signaling itself has been proposed to synergistically contribute to the neuroendurance processes underlying depression (Gardner et al., 2003; Burnett et al., 2005) and neurodegenerative diseases (Lin and Beal, 2006; Mancuso et al., 2007; Petrozzi et al., 2007). Similarly, high baseline oxidative stress could be an intrinsic characteristic of vulnerable neuronal populations. Notably, neuronal nitric oxide synthase (nNOS) and NADPH diaphorase (NADPHd), two enzymes that produce reactive oxidative species, are extensively and almost exclusively co-localized with somatostatin and neuropeptide Y (Dun et al., 1994; Figueredo-Cardenas et al., 1996; Jaglin et al., 2012), hence providing a neurochemical basis for high susceptibility of somatostatin-expressing neurons to generate oxidative stress in response to pathophysiological insults.

**HIGH DEPENDENCE ON NEUROTROPHIC ENVIRONMENT**

Brain-intrinsic neurotrophic factor (BDNF) and its receptor neurotrophic tyrosine kinase receptor type 2 (TrkB) have been implicated in mood disorders (Guiloux et al., 2012; Tripp et al., 2012). BDNF-TrkB signaling is one of the key mediators for maintaining normal somatostatin gene expression (Glorioso et al., 2006; Martinowich et al., 2011). Progressively impairing BDNF-TrkB signaling in patients with mood disturbances may directly impact the biology of somatostatin-expressing neurons, resulting in somatostatin deficits. In addition, Bdnf-TrkB signaling itself is vulnerable to increased inflammation (Goshen et al., 2008; Koo et al., 2003; Burnett et al., 2005) and neurodegenerative diseases (Lin and Beal, 2006; Lotrich et al., 2007). Somatostatin released from sensory nerves and somatostatin receptors on peripheral blood mononuclear cells play a crucial role in anti-inflammation through inhibition of pro-inflammatory peptide release (Szolcsanyi et al., 1998; Kurzatowska and Pawlikowski, 2000; Helies et al., 2004). Rats with chronic inflammation induced by lipopolysaccharide show decreased hippocampal somatostatin expression (Gavilan et al., 2007). It is possible that there is crosstalk among peripheral inflammation, somatostatin function, and central effects of somatostatin-expressing neurons. Hence, decreasing somatostatin expression due to cellular impairment in the progress of neurological diseases may further enhance inflammation in a vicious cycle, leading to exacerbated cellular vulnerability of somatostatin-expressing neurons.

Aging is associated with a considerable increase in an activated, pro-inflammatory state (Wei et al., 1992; Braunsgaard and Pedersen, 2003), a decline in circulating levels of Bdnf (Erickson et al., 2010), and increased oxidative damage (Sohal and Weindruch, 1996). Somatostatin expression is significantly decreased with age in human cortical regions, but parvalbumin expression is not altered by age (Eraji-Benchekroun et al., 2005; Glorioso et al., 2011). Similarly, the number of hippocampal somatostatin-expressing interneurons decreases in aged rats, but the number of parvalbumin-expressing neurons remains the same (Vela et al., 2003). Somatostatin and IL-1β mRNA expression are negatively correlated in aged hippocampus of rats (Gavilan et al., 2007). Comparing the effects of aging on somatostatin expression in the sgACC, an accelerated reduction is found in patients with MDD compared to normal aging subjects (Tripp et al., 2012), suggesting a pattern resulting in an early aging phenomenon which we have speculated may be synergistically induced by normal age-related changes and depression-related pathological change (Douillard-Guiloux et al., 2013).

**CONCLUSION**

Here we have focused on somatostatin, a GABA marker, down-regulated in MDD, schizophrenia, bipolar disorder, and neurodegenerative diseases. Exploring cross-disease molecular (somatostatin) and cellular (somatostatin-expressing interneurons) pathological findings suggests a dimensional pathological phenotype that is specific to the somatostatin gene/cell biological entity rather than to categorical brain disorders. Based on these results we speculate that common risk factors affecting somatostatin and somatostatin-expressing neurons may impact information processing in the cortical local circuits (Figure 1). Clarifying the role of somatostatin and its regulation of GABA inhibition in affect regulation could provide new strategies for predicting, delaying, and treating neurological diseases with mood disturbances. A number of questions remain. For example, are the prevalent somatostatin deficits seen in multiple diseases reflected in a common symptom dimension, such as low mood, across neurological diseases? What are the critical events that determine the vulnerability of somatostatin-expressing neurons?
neurons? And what are the pathogenic mechanisms that mediate the observed disease-related molecular and cellular phenotypes? One possibility is that inflammation, oxidative stress, aging, and reduced neurotrophic support may all converge to affect somatostatin-expressing neurons. Targeting these pathways may exert neuro-protective effects on somatostatin-expressing neu-
rons, as a potential therapeutic approach with implications for several neuropsychiatric disorders and neurodegenerative diseases.

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