Somatostatinergic systems: an update on brain functions in normal and pathological aging

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Somatostatin is highly expressed in mammalian brain and is involved in many brain functions such as motor activity, sleep, sensory, and cognitive processes. Five somatostatin receptors have been described: sst1, sst2A and B, sst3, sst4, and sst5, all belonging to the G-protein-coupled receptor family. During the recent years, numerous studies contributed to clarify the role of somatostatin systems, especially long-range somatostatinergic interneurons, in several functions they have been previously involved in. New advances have also been made on the alterations of somatostatinergic systems in several brain diseases and on the potential therapeutic target they represent in these pathologies.

Keywords: interneurons, SRIF, GPCR, sst, cortistatin, long-range, Alzheimer’s disease

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FIGURE 1 | Schematic representation of somatostatin-related peptides. SRIF14 and CST14 come from two distinct genes but bind the five mammalian sst receptors. Neuronostatin is encoded by the same gene as SRIF but does not bind SRIF receptors; its effects seem mediated through the melanocortin system. c, rat; m, mouse; h, human.

according to their molecular, physiological, and morphological properties. Immunohistochemical characterization of neuronal populations in rat cortex initially stated, based on calcium-binding proteins and peptides expressions that parvalbumin (PV), SRIF, calretinin, and cholecystokinin labeled four main non-overlapping chemical classes of interneurons (Xu et al., 2006). However, several studies later reported a significant colocalization of SRIF and calretinin in mouse brain (Xu et al., 2006; Kosaka and Kosaka, 2007; Lepousez et al., 2010a), pointing out species-dependent variations in the repertoire of calcium-binding proteins and neuropeptides. It seems that neuronal populations immunoreactive for calbindin or the neuropeptide Y strongly overlap with the somatostatinergic population in rats whereas calretinin is preferentially coexpressed with SRIF in the mouse.

Recent morphological and electrophysiological studies using GIN mice focused on SRIF-expressing populations in cortical circuits. In mouse cortex, parvalbumin- and SRIF-expressing neurons respectively constitute 40 and 30% of the total GABAergic neurons, calretinin being expressed in 50% of the somatostatinergic population (Rudy et al., 2011). The remaining cortical inhibitory interneurons, expressing isotropic serotoninergic receptor SHT3a, include VIP- and NPY-positive subpopulations whose partial colocalization with SRIF has been reported (Gonchar et al., 2007; McGarry et al., 2010). SRIF-positive interneurons are homogeneously distributed in all cortical layers (2–6), as compared to PV-positive inhibitory interneurons that are concentrated in the upper part of the layer (Perrenoud et al., 2012).

The major class of SRIF interneurons, the Martinotti cells, have ascending axons that arborize and spread horizontally in layer 1, targeting the distal dendritic parts of excitatory pyramidal neurons (for review, see Voellet et al., 2009). Excitatory inputs onto Martinotti cells are generally strongly facilitating, allowing feedback inhibition of the excited pyramidal cell that increases as function of the rate and the duration of the presynaptic discharge (Kapfer et al., 2007; Silberberg and Markram, 2007). The relative distance between excitatory and interneurons inputs may also impact feedback selectivity and grade, inhibition being stronger for closer inputs. A recent study using a two-photon microscopy approach coupled to uncaged glutamate in cortical slices of GIN mouse mapped the inhibitory network between SRIF-positive interneurons and pyramidal cells at the single-cell resolution (Fino and Yuste, 2011). Whatever the pyramidal cell stimulated, it led to a dense innervation of the surrounding somatostatinergic interneurons, with activity related to the proximity of the cells. Notably, this inhibitory connectivity looked unspecific as all inhibitory interneurons were locally connected to every sampled pyramidal cells regardless whether these were connected among themselves or not. This dense circuit and the fact that somatostatinergic neurons electrically communicate via gap junctions (Ma et al., 2006; Hu et al., 2011) favors the hypothesis that the entire somatostatinergic population belongs to a same inhibitory cortical circuit, contradicting the hypothesis of specific inhibitory cortical subnetworks.

Additional classes of cortical SRIF inhibitory interneurons have been recently described according to their localization, intrinsic firing properties, expression of molecular markers, and connectivity (Gonchar et al., 2007; McGarry et al., 2010). On one hand, calretinin expression was proposed as a distinctive marker (Rudy et al., 2011), since its expression is associated to distinct neuronal morphology and connectivity in populations with distinct ontogenic origin (Sousa et al., 2009; Xu et al., 2010). On the other hand, two novel SRIF-positive subtypes were identified after cluster and principal component analysis of a whole range of morphological or electrophysiological parameters (McGarry et al., 2010). These cell types have some similarities to neurons labeled in a GABAergic-GFP strain distinct from GIN (X94 strain; Ma et al., 2006), such as the lack of expression in the layer 1, but they target different cortical layers. Future identification of their respective calcium-binding proteins and neuropeptides repertoire as well as their molecular phenotype will help to conciliate these independent classifications based on morphological and electrophysiological properties.
Somatostatin is found in most sensory systems, i.e., retina (Thermos, 2003; Cervia and Bagnoli, 2007). In the olfactory system, SRIF expression has also been described in sparse short-axon cells scattered in the deep part of the granule cell layer (the main site of intrinsic inhibitory neurons; Shapley and Ennis, 1996; Eyre et al., 2009) and in the peripheral glomerular layer (which receives sensory inputs) in some species (Hwang et al., 2004). Recently, a novel type of somatostatinergic interneurons has been described as predominant in the murine olfactory bulb and specific to this species (Lepousez et al., 2010a). SRIF-positive somata and dendritic fields are restricted to the layer of the olfactory bulb where intrinsic GABAergic interneurons and bulbar principal cells interact through dendrodendritic reciprocal synapses to initiate local gamma oscillations responsible for odor processing. Electron microscopy evidences suggest that SRIF-positive interneurons also establish reciprocal dendrodendritic synapses with the bulbar principal cells (mitral cells). SRIF-positive neurons have also been described downstream in the olfactory pathway; SRIF interneurons constitute a major GABAAergic population in the pars principalis of the anterior olfactory nucleus and in the olfactory tubercle (Brunjes et al., 2011). In both piriform and entorhinal cortices, two cortical structures involved in the processing of odor coding, multipolar SRIF-positive interneurons displaying Martinotti-like morphological and electrical properties are found in the deep (Young and Sun, 2009; Saiz-Sanchez et al., 2010; Suzuki and Bekkers, 2010) and
Autoradiographic studies characterized initially two SRIF bind-
wide expression of SRIF receptors in the CNS. In contrast to most
Based on structural, pharmacological, and operational features,
internalization and dimerization properties (Csaba et al., 2012).
Long-range projecting SRIF-containing neurons are encountered
in numerous brain areas (for review, see Viollet et al., 2008)
such as the hippocampus (Jinno et al., 2007), the cerebral cortex
(Tomiska et al., 2005), and the amygdala (McDonald et al., 2012).
For instance, virtually all non-pyramidal neurons in the amygdala
that have long-range projecting axons to the basal forebrain in
the rat express SRIF (McDonald et al., 2012). Figure 3 represents
the projections of all long-range somatostatinergic interneurons
known to date in the brain.

**SOMATOSTATIN RECEPTORS IN THE CENTRAL NERVOUS SYSTEM**

Autoregulatory studies characterized initially two SRIF bind-
ing site according to their affinity for the synthetic agonist
ocreotide and their pattern of expression. In the early 1990s,
five receptors (sst1−5) belonging to the G-protein-coupled recep-
tors (GPCRs) family were cloned and characterized from various
species. Sequence homology is 39−57% among the five subtypes,
each being highly conserved across species. They activate mul-
tiple intracellular targets (Olias et al., 2004) and display distinct
internalization and dimerization properties (Casba et al., 2012).
Based on structural, pharmacological, and operational features,
they are now divided into two groups displaying nanomolar affin-
ity for both SRIF and CST: SRIF-1 (sst1, sst3, and sst5 receptors) and
SRIF-2 (sst2 and sst4 receptors). Figure 2B represents the wide
eexpression of SRIF receptors in the CNS. In contrast to most
GPCRs, sst2−5 are unique because their gene coding sequence is
devol of introns. However, this does not preclude the generation
of spliced variants such as a shorter isoform of mouse sst2, named
sst2Δext, originating by the excision of a cryptic intronic sequence
(Vanetti et al., 1992), and spliced variants of sst3 in human and
rodents (Córdoba-Chacón et al., 2011). While some data suggested
that CST also acts through the prion protein in dendritic spines
and pre-synaptic release onto dendritic shafts of principal neurons,
increases and prolongs GABA effect. This presynaptic action on Ca2+
conductance could explain, at least in part, the inhibitory effect of SRIF on long-
term potentiation in the mouse dentate gyrus (Baratta et al., 2002). By these inhibitory effects on
excitatory synaptic transmission, SRIF, co-released with GABA
on dendritic shafts of principal neurons, increases and prolongs
GABA effect. This presynaptic action on Ca2+ conductance could
explain, at least in part, the inhibitory effect of SRIF on long-
term potentiation in the mouse dentate gyrus (Baratta et al.,
2002). Other studies suggest that presynaptic R2 channels mod-
ulation may also be involved in the SRIF inhibition of excitatory
transmission (Tallent and Siggins, 1997). More precisions on the
mechanisms have been given by Grilli et al. (2004), demonstrat-
ing on synaptosomal preparations from mouse cerebral cortex that
activation of sst2 presynaptic receptors may inhibit the CAMP/PKA
pathway stimulated by high potassium concentration, leading to
a decrease of the evoked glutamate release. If in the hippocam-
pus, cortex and other neurotransmitter systems, the presynaptic effects of SRIF concern almost exclusively the excitatory transmission (Ponceau et al., 2003), SRIF is also able to decrease GABA release in different brain structures, such as the rat basal forebrain (Momiyama and Zaborszky, 2008), the neostriatum (Lopez-Huerta et al., 2008), and the thalamus (Leresche et al., 2006). In the basal forebrain, SRIF presynaptically inhibits both GABA and glutamate release onto cholinergic neurons in a Ca2+-dependent way.
FIGURE 3 | Schematic representations of long-range somatostatinergic interneurons in the central nervous system. (A) Telencephalic efferent projections to the rest of the brain. (B) Efferent projections arising from the diencephalon and projecting to the telencephalon and the pons. (C) Efferent projections arising from the mesencephalon, the medulla oblongata, the pons and the spinal cord. Entoped, entopeduncular; BLA, basolateral amygdala; BST, bed nucleus of the stria terminalis; CEA, central amygdala; DG, dentate gyrus; DRG, dorsal root ganglia; MPDA, median preoptic area; NTS, nucleus of the solitary tract; OB, olfactory bulb; PAG, periaqueductal gray; POA, preoptic area; PVN, paraventricular nucleus.
Postsynaptic mechanisms

Effects of SRIF on intrinsic neuronal membrane properties are well documented. Somatostatin induces a membrane hyperpolarization resulting from the activation of two distinct K⁺ currents, the voltage-sensitive K⁺ current or M-current (Iₐ,M; Moore et al., 1988; Jiang et al., 2003), and a voltage-insensitive leak current (Schweitzer et al., 1998). In hippocampal CA1 pyramidal neurons, sst₂ seems to be the receptor subtype that couples to Ca²⁺-activated K⁺ currents (SK-channels) and activates large conductance g(K)Ca²⁺ (GK channels). These results highlight the fact that SRIF is a regulator of cellular function in the striatum. The numerous effects of SRIF on Ca²⁺ and K⁺ channel conductance in different structures are reviewed by Cervia and Bagnoli (2007).

A huge amount of literature has tried to define the pharmacological nature of SRIF effects, using agonists and antagonists of SRIF receptors or mice invalidated for receptor subtypes. Results are often controversial and are different in mice and rats (Aourz et al., 2011). Therefore, the classification of SRIF effects is complex and it is accentuated by the description of functional cooperation between different receptor subtypes sst₁/sst₃, sst₂/sst₄, sst₃/sst₄ (Moneta et al., 2002; Gastrambide et al., 2010; Aourz et al., 2011). Recent publications suggest that sst₃ and sst₄ (but not sst₁; de Bundel et al., 2010) have potent anticonvulsant properties (Aourz et al., 2011), and that sst₃, the major receptor subtype involved in the anticonvulsant effect of SRIF in the hippocampus exerts a functional cooperation with sst₁/sst₃. In hippocampus, sst₃ activation inhibits both NMDA- and AMPA-mediated responses but did not affect the inhibitory transmission (Cammalleri et al., 2009).

SRIF-containing neurons are involved in physiological functions

Interneurons

A large diversity of inhibitory interneurons is able to exert inhibition on specific compartments of principal cells. Among these populations is the dendrite-targeting SRIF-expressing interneuron located in oriens-lacunosum molecular of the hippocampus. These SRIF-containing neurons are the only subtype of interneuron that reliably follows synaptic stimulation of the afferents in the theta frequency range via activation of their kainate receptors, suggesting that they play an important role in theta band frequency oscillations (Goldin et al., 2007). Spontaneous activities of inhibitory interneurons have been characterized and SRIF-containing neurons are described in the cortex and piriform cortex as regular-spiking (Kawaguchi and Kubota, 1999; Suzuki and Bekkers, 2010) or low-threshold spiking neurons (Goldberg et al., 2004), often opposed to the fast spiking PV-containing neurons. In the hippocampus, SRIF neurons are locked to the ascending phase of the theta cycle. However, using an optogenetic inhibition of different populations of interneurons, it was recently demonstrated that silencing SRIF interneurons increases burst firing of pyramidal cells without altering the theta phase of spikes (Royer et al., 2012). Applying optogenetic technique to animals trained to run head-fixed on a treadmill belt rich with visual–tactile stimuli, these authors provided evidence that the dendritic (but not somatic) inhibition of pyramidal neurons by SRIF interneurons is critical for controlling spike burst firing during active exploration. They concluded that perisomatic PV-targeting interneurons control the spikes’ theta phase while the dendrite-targeting SRIF interneurons control the rate of discharge. This is in agreement with the fact that dendritic but not somatic GABAergic inhibition is decreased in experimental epilepsy (Cossart et al., 2001). Combining optogenetic stimulation with in vivo two-photon imaging in the mouse visual cortex, Wilson et al. (2012) demonstrate that soma-targeting PV neurons regulate the gain of cortical response, while dendritic-targeting SRIF neurons shift response level and alter stimulus selectivity, leaving response gain unaffected.

Another demonstration of the role of SRIF interneurons in cellular function has been given recently (Geret et al., 2012). In this study, SRIF neurons recorded in the barrel cortex of awake mice were tonically active during quiet wakefulness but they decreased their firing during whisker sensorimotor processing. This decrease in firing relieves the dendrites of excitatory pyramidal neurons from inhibition.

It is known that inhibitory neurons have diverse roles in physiological and synaptic function, based on their connectivity patterns and intrinsic properties. All the experiments described above demonstrated that SRIF interneurons have a prominent role in the regulation of distal dendrites excitability.

Long-range projecting neurons

The long-range projecting somatostatinergic non-pyramidal cells found in the hippocampus target the medial septum and the medial entorhinal cortex (Violette et al., 2008; Melzer et al., 2012) and more specifically form inhibitory synapses on GABAergic interneurons of these areas. They coordinate activity between distant brain regions, contributing to the generation and the synchronization of rhythmic oscillatory activity in the hippocampus and entorhinal cortex (Melzer et al., 2012). They are therefore involved in spatial and temporal coding. Interestingly, early-generated GABA-containing hub neurons, dendrite-targeting interneurons, express preferentially SRIF and give long-range projecting neurons (Picardo et al., 2011). These superconnected hub cells are present early in the developing hippocampus. They develop a widespread axonal arborization and remain into adulthood. They play a key role in the control of the hippocampal giant depolarizing potentials as well as in the modulation of network dynamics. In the other brain areas, the precise contribution of these long-projecting SRIF neurons in the oscillatory activity still needs to be addressed.

Hypophysiotropic neurons

Somatostatin release inhibiting factor was initially discovered as a neurohormone that inhibits GH secretion from anterior pituitary somatotroph cells. This function is exerted by hypophysiotropic neurons, located in the anterior periventricular hypothalamic nucleus, which project to the median eminence and release the peptide in the fenestrated capillaries of the hypophalamo-hypophysial portal vessels; thus directly connecting the brain to the pituitary.
the anterior pituitary. SRIF is also a potent inhibitor of many hormonal and exocrine secretions as well as an antiproliferative agent in normal and tumoral tissue (Uppelbaum, 1986). SRIF analogs (octreotide and lanreotide) have potent inhibitory effects on hypersecretion, thereby alleviating the symptoms associated with neuroendocrine tumors. Furthermore, the antitumor potential of octreotide is now well documented. Pasireotide, a long-acting SRIF analog, has the advantage of targeting a wider range of SRIF receptors (subtypes 1, 2, 3, and 5) than the analogs previously used in clinical practice (which preferentially target subtype 2) and has a broader spectrum of activity (for review, see Bouaquet et al., 2012).

INVOLVEMENT OF SRIF SYSTEMS IN SENSORY, MOTOR, AND COGNITIVE FUNCTIONS

Since SRIF systems are widely expressed in CNS, they are involved in numerous functions including nociceptive and vasoconstrictor properties. Here, we will present recent advances about the role of SRIF systems in autonomic responses (digestion, cardiac rate, and respiration) and motor functions as well as cognitive functions such as learning and memory and emotion (for review, see Voillet et al., 2008).

Somatostatinergic involvement in sensory functions

Somatostatinergic systems are expressed in mammalian retina (for review, see Thermos, 2003; Casusi et al., 2005; Cervia et al., 2008), where it is suspected to exert multiple actions on neurons and on retinal physiology. SRIF acts as a positive factor in the retina by regulating homeostasis and protecting neurons against damage. Both sst2 and sst5 somatostatinergic receptors are involved. Indeed, activation of sst2 protects the retina from ischemic insults ex vivo (Mastrodimou et al., 2003) and sst4 as well as sst5 receptor activation protect from excitotoxicity in vivo (Kagiadaki and Thermos, 2008; Kagiadaki et al., 2010; Kohno et al., 2012). The severity of angiogenic responses to hypoxia is correlated to the sst2 expression level in the retina (Dal Monte et al., 2007). Moreover, the sst5-prefering agonist octreotide prevents hypoxia-induced VEGF up-regulation (Dal Monte et al., 2009).

Somatostatinergic modulation of olfactory discrimination

Recent studies have shown that SRIF modulates olfactory processing in mice (Iepouser et al., 2010a,b). In mouse main olfactory bulb, SRIF is mainly concentrated in local GABAergic interneurons synaptically connected to the mitral cells by reciprocal dendrodendritic synapses. When activated by an odor, mitral cells synchronize and generate gamma oscillations of the local field potentials that are involved in olfactory processing. Pharmacological or genetic blockade of sst4 transmission in the olfactory bulb of awake animal selectively decreased the gamma oscillations power while pharmacological activation of sst4 had opposite effects. These treatments were respectively correlated to either impairment or improvement of odor discrimination performances of the pharmacologically injected animals. Thus, bulbar endogenous SRIF, presumably released from external plexiform layer interneurons, affects gamma oscillations through the dendrodendritic reciprocal synapse and contributes to olfactory processing.

Involvement of SRIF in learning and memory

It has been reported for decades that SRIF plays a role in learning and memory at different stages of information processing. The first studies investigating its role in cognition showed that intracerebroventricular administrations of SRIF improved learning in active avoidance tasks (Bollok et al., 1983; Vecsei et al., 1983; Vecsei and Widerlow, 1988) and prevented electroshock-induced amnesia in passive avoidance paradigms (Vecsei et al., 1983, 1984). Conversely, the depletion of SRIF in the brain by cysteamine (which depletes SRIF levels; Szaiko and Reichlin, 1981) produced major memory deficits in passive avoidance (Bakhit and Swendlove, 1986; Schettini et al., 1988; DeNoble et al., 1989). These studies revealed that SRIF is involved in the acquisition of information but other studies showed that cysteamine produced memory deficits not only when given before the training session but also within a critical time window (0–4 h) after acquisition, suggesting that SRIF plays a critical role in memory consolidation processes (Haronimou et al., 1987, 1989; Schettini et al., 1988; Vecsei et al., 1990).

The hippocampus is an essential structure in learning and memory (Jessen and Squire, 2012), and is also a chosen site to study the effects of SRIF on learning and memory since injection of cysteamine impairs tasks requiring its integrity (DeNoble et al., 1989; Guillou et al., 1994). Surprisingly in the rodent hippocampus, both activation of SRIF receptors as well as depletion of SRIF contents generate hippocampal memory impairments. Indeed, microinjections of cysteamine, SRIF or CST directly into the hippocampus impaired hippocampal-dependent spatial learning (Guillou et al., 1994a, b; Ramirez et al., 2001; Mendez-Diaz et al., 2005; Gastambide et al., 2009). Consistent with these pharmacological results, transgenic mice overexpressing CST display a profound impairment of spatial learning (Tallent et al., 2005). Studies that investigated which SRIF receptor mediates SRIF memory effect showed that intrahippocampal injections of the sst4 agonist, but not sst1, sst2, or sst3 agonists, dramatically impaired spatial memory formation (Gastambide et al., 2009). Importantly, these authors found that concomitantly to the impairment of spatial memory, an sst4 agonist also enhanced the use of striatum-dependent memory. Therefore, it was hypothesized that hippocampal sst4 controls the use of cognitive strategies by switching from hippocampus-based multiple associations to simple striatum-based behavioral response through a functional interaction with sst4 receptor (Gastambide et al., 2010). The precise cellular and molecular mechanisms involved in this functional interaction between sst2 and sst4 are not fully understood but some studies showed that sst4 mediates increases in glutamatergic excitability and bursting frequency, which were blocked by sst4 agonists or antagonists and were lacking in sst4 knockout (KO) mice (Moneta et al., 2002; Cammalleri et al., 2006). Therefore, sst4 is not the unique SRIF receptor in the hippocampus mediating SRIF memory effects as sst4 also modulates memory as previously suggested by Dutar et al. (2002).

Involvement of SRIF in the control of emotion

Somatostatin and its receptors are strongly expressed in the different nuclei of the amygdala (Hannon et al., 2002), a key brain region involved in the control of emotion. SRIF receptors (subtypes 1, 2, 3, and 5) than the analogs previously used in clinical practice (which preferentially target subtype 2) and has a broader spectrum of activity (for review, see Bouaquet et al., 2012).
Involvement of SRIF in locomotion

An involvement for SRIF systems in this area, the effects of SRIF on emotions have not yet been studied extensively. Nevertheless, some studies reported an involvement of SRIF systems in the control of emotion and anxiety. Indeed, some recent work revealed that the pattern of activation of SRIF-positive interneurons was specific to the nucleus of the amygdala considered and also to the kind of stressor used (Butler et al., 2012). Moreover, SRIF has anxiolytic- and antidepressant-like effects (Engin et al., 2015) that are associated with the suppression of the frequency of hippocampal theta activity, a neurophysiological signature common to most classes of anxiolytic drugs (i.e., benzodiazepines, selective 5-HT reuptake inhibitors, 5-HT1A agonists). These effects seem to be mediated by sst2 receptor since both intra-septal and intra-amygdala SRIF microinjections induced anxiolytic effects that were completely reversed by selective sst2 receptor antagonist injection in these brain areas (Young and Treit, 2012). Additional evidence for a specific role of sst2 receptor came from the observation that a stressful experience is associated with an increase of sst2 mRNA levels within the amygdala (Nanda et al., 2008) and that mice lacking sst2 receptor display increased anxiety-like behaviors associated with increased pituitary ACTH levels, a main regulator of the stress response (Violett et al., 2000).

Somatostatinergic networks in pathological conditions

Involvement of SRIF in locomotion

An involvement for SRIF was also reported in motor functions. Increased motor activity was shown in rats receiving intracerebroventricular administration of SRIF (Havlíček et al., 1976) as well as in mice receiving unilateral striatal infusions of the peptide by retrodialysis (Hathaway et al., 2004) and in animals receiving direct injections of SRIF in the nucleus accumbens (Raynor et al., 1993). Tashiev et al. (2001) showed that SRIF modulated locomotor activity in biphasic manner. Indeed, shortly after SRIF striatal injection a decrease of locomotor activity is observed whereas later, the locomotor behavior is increased. Similar effects have been found after striatal injection of sst2 and sst3 agonists. On the other hand, genetic invalidation of sst2 receptor in two different strains of mice as well as SRIF null mice showed an impairment of motor functions (Violett et al., 2000; Zeyda et al., 2001; Allen et al., 2003). But the role of SRIF in locomotion seems to be limited to fine motor control since these different lines of transgenic mice only develop impaired motor coordination in tasks that require a fine motor control and display normal levels of motor activity and coordination in undemanding tasks (Violett et al., 2000; Zeyda et al., 2001; Allen et al., 2003).

Autonomic responses

Somatostatin release inhibiting factor and its receptors are found in several medullary oblongata nuclei that control autonomic functions such as digestion, cardiac rate, and respiration (Llona and Eugenín, 2005; Spary et al., 2008; Violett et al., 2008). In the preBötzinger complex (preBöC), a critical component of the respiratory rhythm generator that underlies mammalian breathing, SRIF is expressed in a subpopulation of glutamatergic neuropeptide Y receptor positive neurons, a kind of neuron rhythmically active (Stornetta et al., 2003). Originating from the homeogene Dbx1 lineage, these cells are mandatory for breathing, since inactivation of the Dbx1 gene impaired their differentiation and disrupted respiratory rhythm generation in the preBöC (Boeurier et al., 2010; Gray et al., 2010). Acute silencing of somatostatinergic preBöC neurons increased respiratory rhythm, leading to persistent apnea (Tan et al., 2008). Similar effects were found in vivo after pharmacological blockade of sst2 transmission, while exogenous SRIF application decreased rhythms generation (Pantaleo et al., 2011; Ramírez-Jarquín et al., 2012). This demonstrated that the peptide exerts a tonic inhibitory control on the rhythmonicogenics in order to avoid deleterious over-activity, probably through cellular subdomain-specific inhibitory and excitatory synaptic contacts (Wei et al., 2012). The existence of long-range somatostatinergic projections to either contralateral preBöC (Stornetta et al., 2003) or downstream premotor neurons (Tan et al., 2010) favors a neuromodulatory role for Pre-BöC SRIF (Llona and Eugenín, 2005), whose developmental impairment may be involved in human pathologies (Schwarzacher et al., 2011) such as the sudden infant death syndrome (Lavezzii and Matturri, 2008).

Somatostatinergic networks in pathological conditions

In animals, an alteration of SRIF systems is observed during normal aging (Stanley et al., 2012) and pathological models of aging. In human a similar specific dysregulation is observed in normal pathological disorders such as some neurodegenerative and psychiatric diseases (Glorioso et al., 2011; Gleichmann et al., 2012).

Alzheimer’s disease

Somatostatin has been involved in Alzheimer’s disease (AD) pathology for a number of years. Indeed, since the early 1980s, it is known that SRIF levels in cortex and hippocampus are decreased in AD patients (Davies et al., 1980). Later, it was demonstrated that the decline in SRIF concentrations in the CSF (Tammenga et al., 1987) or in the middle frontal gyrus (Dournaud et al., 1995) correlates with cognitive deficits. Using quantitative real-time PCR, a recent study confirmed this decrease of SRIF in the inferolateral, medial, and superior temporal lobe of AD patients (Gahete et al., 2010). Interestingly, SRIF concentrations were reported to be significantly lower in Alzheimer patients carrying the epsilon 4 allele of APOE (Grossetelle et al., 1998), the main genetic risk factor described to date for late-onset AD (Genin et al., 2011). In addition, two different studies found in Finnish and Chinese patients that polymorphisms in the SST gene are associated with the risk of developing AD (Vepsäläinen et al., 2007; Xu et al., 2009).

Regarding SRIF receptors, data are limited and controversial. Although all studies agreed on a decrease of SRIF receptors in AD, controversies appeared about the proportion, the localization, and receptor subtype specificity of this decrease. SRIF receptor quantification using quantitative real-time PCR in AD temporal lobe showed a decrease of sst1, sst3, and sst5 receptors whereas sst2 and sst4 receptors were unchanged (Gahete et al., 2010). Previously, an immunohistochemistry study reported a similar decrease of sst4 but showed a reduction in neuronal sst3 – and a modest
decrease in sst-1–like immunoreactivity without any changes in sst-3 immunoreactive neurons (Kumar, 2005). Surprisingly, in the same study, an increase of sst-5 subtype was observed in AD cortex. A radioligand binding and functional study showed a general receptor decrease in AD brain (Beal et al., 1985). More specifically, receptors levels in the frontal and temporal cortex were reduced by approximately 50% of control values in AD patients while a 40% reduction was reported in the hippocampus and no significant changes were found in the cingulate cortex, postcentral gyrus, temporal pole, and superior temporal gyrus. Another radioligand binding study revealed that while the maximal binding capacity of the SRIF-1 receptor subtype (primarily sst2, and possibly sst5) is altered in frontal and temporal cortices, other putative cortical SRIF receptor classes (SRIF-2 sites, i.e., sst4, sst3 and sst4) are not as broadly affected (Kramnik et al., 1992). Finally, a last study showed a significant decrease only in the frontal cortex, but not in other brain regions (Bergstrom et al., 1991). Because of the cholinergic hypothesis regarding AD etiology, it was concluded that the pattern of change of SRIF binding in AD cortex might be secondary to the degeneration of SRIF receptor-bearing cholinergic afferents arising from the nucleus basalis. In line with this idea, experiments in the literature demonstrate that the selective destruction of cholinergic neurons of the basal forebrain with intracerebroventricular injection of 192-IgG-saporin produces an irreversible loss of SRIF-immunoreactive neurons in the hilus of the hippocampus (Jolkkonen et al., 1997) and in the cortex (Zhang et al., 1998). This last study shows a correlation between the intensity of acetylcholinesterase in the cortex and the number of remaining SRIF cells. These data highlight a trophic dependence of SRIF neurons on cholinergic inputs and are consistent with observations in AD and aging.

Although SRIF deficit is not correlated with the amyloid load in AD brain patients (Dournaud et al., 1995), SRIF was identified as a modulator that increases brain norepinephrine activity, one of the main enzymes involved in Aβ degradation (Saito et al., 2005). Recently, it has been shown that neuropeptide pituitary adenylate cyclase-activating polypeptide slows down AD-like mechanisms leading to AD and suggest that SRIF and its receptors are potential pharmacological targets for AD. Indeed, FP962, which promotes SRIF production in the brain, co-administrated with donepezil, an acetylcholinesterase inhibitor widely used to treat patients, enhances cognition in rat and has been proposed as an add-on therapy for AD (McCarthy et al., 2011). In addition, Rubio et al. (2012) recently suggested that SRIF and CST act as a protective agent against Aβ toxicity. However, in an APP transgenic mouse model, data concerning SRIF-containing interneurons are contradictory. In the triple-transgenic model of AD, 3xTg-AD, inhibitory neurotransmission is unchanged in the cerebral cortex and hippocampus (Gleichmann et al., 2012). In a APP/PS1 mouse model of AD, as soon as 6 months of age, a decrease in the number of oriental-lacunosum molecular hilar perforant path-associated SRIF-positive interneurons was evidenced in the hippocampus, when no change was demonstrated for 21 additional mRNA markers tested (Ramos et al., 2006). In the APP/PS1ΔE4 mouse model, Aβ deposition disrupted cognitive circuits when the cholinergic and somatostatinergic systems remained relatively intact (Savonenko et al., 2005). Another study on this last model even found that, in most brain regions tested, SRIF concentrations were increased rather than decreased relative to controls (Hor- gan et al., 2007). Thus, the validity of a direct and major role for SRIF in the regulation of Aβ42 degradation remains to be further confirmed (Iwata et al., 2005). More recent studies, focusing on olfaction, an early-affected function in AD (Wilson et al., 2009), account for evidence of a relationship between Aβ pathology and SRIF alterations in the disease. Indeed, SRIF interneurons and receptors are selectively reduced by approximately 50% in the anterior olfactory nucleus of AD patients (Suárez-Sánchez et al., 2010). These authors suggested that SRIF decreases in AD might be linked with Aβ. Moreover, an increase in the levels of aggregated Aβ peptide is observed with aging in olfactory cortices of APP/PS1 transgenic mouse model of AD, and it is accompanied by a fall in numbers of SRIF-positive interneurons (Suárez-Sánchez et al., 2012).

Experiments from our laboratory demonstrated that intrahippocampal injections of Aβ in rats induced abortive inhibitory septo-hippocampal network activity associated with an impairment of hippocampal memory processes (Villette et al., 2010). This effect can be explained by the selective loss of long-range hippocampal-septal projecting neurons population containing calbindin and SRIF (Villette et al., 2012). This population of SRIF neurons could be a favored target for Aβ, explaining the early decrease of SRIF observed in AD.

Somatotropin release inhibiting factor is not only interacting with Aβ42 in AD, it has also an effect on Tau phosphorylation. Rubio et al. (2008) indicated that in mouse cortex SRIF and CST induce Tau phosphorylation at Ser262, a site modified in AD patients, although with different kinetics. An sst5/sst6 interaction seems implicated in this process but the types of phosphatases that are involved remain to be determined. Moreover, in human apoE4 knock-in mice where Tau phosphorylation and intracellular neurofibrillary tangle-like deposits are detected (Huang et al., 2001; Harris et al., 2003; Brecht et al., 2004), Huang’s group showed that the number of SRIF-positive interneurons correlated inversely with the performance of these mice in a spatial memory task (Andrews-Zwilling et al., 2010).

**PARKINSON’S DISEASE**

Alteration of SRIF levels is also observed in other neurodegenerative diseases. Indeed, decrease in SRIF levels has been described in demented Parkinson’s disease patients (Eppelbaum et al., 1989) as well as in a unilateral 6-OHDA experimental mouse model of Parkinson’s disease (Wilson et al., 2009). Recent data obtained in a rat model of Parkinsonism showed that an alteration of presynaptic modulation by SRIF after dopamine deprivation. This
observation may underlie a homeostatic mechanism trying to compensate for the excitability imbalance between direct and indirect basal ganglia pathways found during Parkinson’s disease (Lopez-Huerta et al., 2012).

**MAJOR DEPRESSIVE DISORDER**

Evidence in major depressive disorder (MDD) suggests an impaired excitation/inhibition balance that is potentially mediated by decreased GABA content (Levinson et al., 2010). More specifically, Shibue et al. (2011) reported a down-regulation of SRIF in the dorsolateral prefrontal cortex (PFC), the subgenual cingulate cortices (Tripp et al., 2011), and the amygdala (Guilhoux et al., 2011) of MDD patients. Engin et al. (2008a) and Engin and Trett (2009) revealed an antidepressant effect of SRIF mediated by either sst2 or sst3 receptor and suggested that while SRIF itself is not appropriate for clinical use because of its short half-life and diverse range of effects (Pinter et al., 2008), a closely related SRIF derivate may have some potential for the pharmacological treatment of depression.

**SCHIZOPHRENIA**

One of the most consistent findings in schizophrenia neuropathology is deficits in cortical inhibitory interneurons across multiple cortical regions (Hashimoto et al., 2008). It has been known for years that cerebral cortical concentrations of SRIF are reduced in schizophrenics (Roberts et al., 1983) as well as hippocampal concentration (Ferrier et al., 1983; Konradi et al., 2011). Moreover, Hashimoto et al. (2008) found that subjects with schizophrenia exhibited deficits in SRIF expression in the PFC, and this was further confirmed after global analysis from six previously published microarray studies (Pere-Santiago et al., 2012). A recent study suggested that this decrease of SRIF-positive inhibitory interneurons in the PFC may be related to changes in an inflammatory response pathway that are often observed in schizophrenics (Fallman et al., 2012). In addition, Reniet et al. (2012) showed that SRIF neurotransmission in the PFC of subjects with schizophrenia is also altered at the postsynaptic level in a receptor subtype-, layer-, and cell type-specific manner. The expression of sst3, but not sst1, mRNA is preferentially lower in layers 5–6, and in larger, putative pyramidal neurons in those layers. These authors suggested converging pre- and postsynaptic mechanisms to reduce inhibitory neurotransmission in pyramidal neurons in the PFC, which could alter the synchronization of low frequency oscillations and disturb working memory performance in subjects with schizophrenia.

**EPILEPSY**

Somatostatin is highly expressed in brain regions associated with seizures and has been implicated as playing a prominent role in epilepsy (Vezzani and Hoyer, 1999) based on the observation of an activity-dependent release of SRIF during seizures, the modulation of SRIF mRNA expression, peptide and receptors levels by seizures and the effect of SRIF and its analogs on seizures (Tallent and Qiu, 2008; Zafar et al., 2012). Temporal lobe epilepsy (TLE) is characterized by hippocampal sclerosis together with profound phenotypic changes of different classes of interneurons. Hilar SRIF interneurons undergo extensive degeneration in patients with hippocampal sclerosis (de Lanerolle et al., 1989, Robbins et al., 1991). Recently, this selective neurodegeneration has been linked to the specific enrichment of somatostatinergic neurons in striatum-enriched phosphatase, an enzyme that counteracts the MAPK neuroprotective pathway (Choi et al., 2007; Florio et al., 2008). SRIF receptors may represent potential therapeutic targets for TLE. Indeed, SRIF is released in characteristic conditions of seizures and SRIF and its analog affect seizures (Vezzani and Hoyer, 1999; Backmaster et al., 2002). However, information on the precise contribution of each SRIF receptor on the SRIF-induced inhibition of epileptiform activity is still limited. Although the sst3 receptor is likely to mediate the anticonvulsant effects of SRIF in rat hippocampus (Vezzani and Hoyer, 1999), observations in the mouse support a central role for sst4 (Moneta et al., 2002) and/or sst3 receptors (Zanolla et al., 2004, 2006) in mediating SRIF inhibition of epileptiform activity. In a rodent model of cortical focal ischemia, sst3 is also activated while the infarct size is significantly reduced in sst3 KO mice (Stumm et al., 2004). However, recent data in rats showed that sst3 receptors do not appear to mediate the in vivo anticonvulsant effect of SRIF (de Bundel et al., 2010), whereas sst3 and sst4 mediate this effect through a functional interaction with sst2 receptor (Anast et al., 2011).

**CONCLUSION**

Somatostatin systems are widely expressed in the different brain regions and are involved in numerous processes from sensory to cognitive functions, suggesting that they play major roles in brain functioning. These key roles are illustrated by the decrease of SRIF concentrations observed in neurodegenerative diseases such as AD and Parkinson’s disease but also in psychiatric diseases such as schizophrenia and MDD. From this perspective, SRIF systems represent a potential and challenging therapeutic target. Further studies need to be carried on to unravel the role of SRIF systems in all functions they have been implicated in.

**ACKNOWLEDGMENTS**

Supported by NRf post-doctoral fellowship (to Guillaume Martel), ANR-10-MALZ-003-01 SOMADOLF and Fondation Recherche Plan Alzheimer.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.