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**Somatostatinergic systems in brain: networks and functions.**

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**Summary**

Somatostatin is abundantly expressed in mammalian brain. The peptide binds with high affinity to six somatostatin receptors, sst1, sst2A and B, sst3 to 5, all belonging to the G protein-coupled receptor family. Recent advances in the neuroanatomy of somatostatin neurons and cellular distribution of sst receptors shed light on their functional roles in the neuronal network. Beside their initially described neuroendocrine role, somatostatin systems subserve neuromodulatory roles in the brain, influencing motor activity, sleep, sensory processes and cognitive functions, and are altered in brain diseases like affective disorders, epilepsy and Alzheimer's disease.

**1. Introduction**

Somatostatin<sub>14</sub> (SRIF: somatotropin release inhibiting factor) was serendipitously discovered in 1972 by Roger Guillemin and his colleagues who were trying to purify and characterize growth hormone (GH)-releasing hormone (GHRH) (Brazeau et al., 1973). Soon thereafter, an amino-terminally extended peptide, SRIF<sub>28</sub>, was purified from the gut. Both peptides were found in the nervous system, where SRIF<sub>14</sub> is the predominant form (for review, Epelbaum 1986). Using iodinated somatostatinergic ligands, two pharmacologically

distinct binding sites were found in the brain. Later, six somatostatin receptor (sst) subtypes, named sst1, sst2A, sst2B, sst3, sst4 and sst5, and belonging to the G-protein-coupled receptor family, were cloned and divided into two subfamilies, based on their pharmacological and molecular characteristics (for review, see Hannon et al., 2004, Olias et al., 2004). Many transduction mechanisms have been described in transfected systems (for review see Lahlou et al., 2004, Olias et al., 2004), however most physiological actions of the native receptors *in situ* remain to be established. The generation of specific antibodies against each somatostatin receptor revealed a definite cellular and subcellular localization of somatostatin receptor subtypes in the central nervous system (CNS). The development of specific somatostatin analogues and antagonists (Hannon et al., 2004, Engström et al., 2006) together with the availability of genetically modified animal models (Allen et al., 2003, Kreienkamp et al., 1999; Strowski et al., 2003, Videau et al., 2004, Zeyda et al., 2001, Zheng et al., 1997) contributed to a better understanding of the individual somatostatin receptor characteristics *in vivo*, and their specific roles in brain functioning. This review summarizes the latest advances concerning the anatomical and functional characterization of central somatostatinergic networks as well as their physiopathological implications in CNS diseases.

## 2. Somatostatinergic networks in the brain

### 2.1. Central somatostatinergic systems

SRIF-immunoreactivity is found in many neurons in the mammalian brain including humans. High immunoreactivity is found in the mediobasal hypothalamus and median eminence, amygdala, preoptic area, hippocampus, striatum, cerebral cortex, olfactory regions, and the brainstem. Two main categories of somatostatinergic neurons can be distinguished: those which project to a distance from their soma (*long-projecting neurons*) and short GABAergic neurons (*interneurons*) acting within microcircuits.

*Long-projecting somatostatinergic neurons.* Some recently described long-projecting somatostatinergic neuronal systems have complemented or refined the classical ones and are described in Table 1.

- *The hypothalamic-hypophysiotropic system:* somatostatin neurons from the periventricular nucleus (Pev) and the parvocellular paraventricular nucleus of the hypothalamus project to the median eminence where they make contacts with the

fenestrated capillary loops of the portal vasculature, from which the peptide directly reaches pituitary cells. Cocaine-amphetamine-regulated transcript (CART) is colocalized in 38% of these neurons. Somatostatin cells in the periventricular nucleus also innervate many limbic (olfactory tubercle, septum, habenula, hippocampus) and mesencephalic (substantia nigra, locus coeruleus) regions.

- *The amygdaloid-bed nucleus of the stria terminalis (BNST) systems*: Two projection systems arise in the amygdala. Thirty percent of the lateral amygdala projecting neurons are somatostatinergic and they innervate distant regions (preoptic hypothalamic area) as well as the different amygdala nuclei, except the central nucleus. From this latter nucleus originates the second amygdalar somatostatinergic projecting system involved in emotion control : it innervates directly - or indirectly through the BNST - many brainstem regions implicated in vegetative functions, such as the parabrachial nucleus (visceral sensibility), the dorsal motor nucleus and the nucleus of the solitary tract (cardiovascular regulation). Somatostatinergic neurons of the solitary tract nucleus, the only ones in the brain to contain only SRIF<sub>28</sub>, also relay visceral controls through their projections to the ambiguous nucleus (oesophagean motility) and parabrachial nucleus. Lastly, solitary tract nucleus, parabrachial nucleus, pedunculopontine nucleus and, to a lesser extent, other brainstem nuclei send somatostatinergic projections to the medial preoptic area and paraventricular nucleus of the hypothalamus and may influence vegetative functions, sexual behaviour and autonomic system.
- *The neuromodulatory monoaminergic systems* : Tract-tracing analysis coupled with immunohistochemistry confirmed that a subset of locus coeruleus noradrenergic-projecting neurons and of raphe nucleus serotonergic-projecting neurons contains somatostatin.
- *The hippocampo-septal pathway* : Rhythmically bursting GABAergic septo-hippocampal neurons are innervated by somatostatinergic hippocampo-septal neurons.

Two novel long-projecting systems have been reported using tract-tracing methods. Besides the classical connections of hippocampal CA3 and dentate gyrus principal cells with the contralateral hippocampus, nearly all hilar somatostatinergic interneurons have also commissural projections (Zappone et al., 2001). A second study (Tomioka et al., 2005) revealed a network of long-range cortico-cortical projections within the mouse neocortex and

established that these projecting neurons were nearly all somatostatinergic interneurons. These two latter studies, together with the analysis of hippocampo-septal neurons (Gulyas et al 2003), outline the fact that some somatostatin cells, usually considered as local interneurons, can also send long-range projections.

*Somatostatin interneurons within microcircuits: new advances in hippocampus and neocortex.* After three decades of somatostatin-immunoreactive interneurons mapping throughout the brain, recent studies have focused on their architecture, connectivity and physiology in order to place them within well-characterized networks such as hippocampus or neocortex. Several studies took advantage of transgenic mice models in which the green fluorescent protein (GFP) gene is under the control of a shortened fragment of the glutamate decarboxylase 67 (GAD67) promoter, which labels exclusively a subpopulation of somatostatin neurons (Oliva et al., 2000, Ma et al., 2006). Table 2 summarizes these recent findings and reveals striking parallels within telencephalic structures.

Firstly, in the neocortex, hippocampus, amygdala, neostriatum and olfactory bulb, somatostatinergic interneurons constitute a subpopulation of GABAergic interneurons (30-50% in hippocampus and neocortex, Markram et al., 2004, Jinno and Kosaka, 2006). The neuronal populations immunoreactive for the calcium-binding protein calbindin or the neuropeptide Y strongly overlap with the somatostatinergic population (Kohler et al., 1987; Gulyas et al., 2003; Markram et al., 2004; Muller et al., 2007), reaching 100% percent colocalization in neostriatum (Tepper and Bolam, 2004). Somatostatin more rarely colocalizes with the calcium-binding proteins calretinin or parvalbumin, with the neuronal nitric oxide synthase (nNOS), and almost never colocalizes with the vasoactive intestinal peptide VIP (Kawaguchi and Kubota, 1998; Gulyas et al., 2003; Jinno and Kosaka, 2004, 2006; Markram et al., 2004; Tepper and Bolam, 2004; Toledo-Rodriguez et al., 2005). Moreover, the somatostatin-related peptide cortistatin is expressed in a subset of GABAergic interneurons in the cortex and hippocampus that partially overlaps with those containing somatostatin (see de Lecea, this issue).

Secondly, in the hippocampus, neocortex, amygdala, neostriatum, basal forebrain, olfactory bulb (Table 2) and retina (Bagnoli, this issue), somatostatinergic interneurons innervate mostly their respective principal cells (see references, Table 2). Two types of somatostatin interneurons with similar architecture and connectivity patterns have clearly been characterized in both hippocampus and neocortex (Fig. 1):

- The predominant cell type, Martinotti cells in the neocortex and Oriens-Lacunosum Moleculare (O-LM) neurons in the hippocampus, display their soma and dendritic tree in the cortical layers II/III to VI and in the stratum oriens, respectively. A proximal dendrite forms an ascending axon which exclusively arborizes in layer I and in the stratum lacunosum-moleculare. In both hippocampus and cortex, axons innervate distal dendrites of their respective principal cells. Martinotti and O-LM somas and dendritic trees also receive inputs from their respective pyramidal cells, resulting in a recurrent inhibitory circuit (Katona et al., 1999, Kapfer et al., 2007). In the dentate gyrus, an equivalent of the O-LM cells, the HIPP cells (Hilar Perforant Path associated cells) show similar architecture: their soma and dendritic tree in the hilus receive inputs from the mossy fibers collaterals, and their axons arborize in the outer molecular layer of the dentate gyrus, where they contact apical dendrites of granule cells and also receive direct excitatory inputs from axonal terminals of entorhinal afferents (Leranth et al., 1990).

- The second cell type, basket cells (SRIF-positive basket cells representing 30-40% of the basket cell population) in the neocortex and Oriens Bistratified (O-Bi) cells in the hippocampus, have their soma and dendritic tree mainly in the cortical layers IV to VI and in the stratum oriens of hippocampus, respectively. The axon arborizes in the same or adjacent layer, innervating proximal dendrites of principal cells.

Beside these structural considerations, both interneuronal types show distinct firing patterns (Markram et al., 2004; Wang et al., 2004) and the principal cells domain specifically innervated by the interneurons is associated with distinct evoked postsynaptic currents (Maccaferri et al., 2000) as well as distinct patterns of sst cellular distribution (Fig. 1).

Similar ontogenic origin of GABAergic interneurons of the hippocampus and the neocortex may account for the striking parallels observed between hippocampal and neocortical somatostatinergic interneurons arrangement. Somatostatinergic interneurons, detected at early stages of ontogenesis in both hippocampus and neocortex (Shiosaka, 1992), mainly derive from a common proliferative zone, the medial ganglionic eminence (reviewed by Wonders and Anderson, 2006). After genetic determination and tangential migration, activity-dependent maintenance of neuropeptide content is mediated by BDNF (Nawa et al., 1994; Große et al., 2005), which may control somatostatin expression and neuropil development even during adulthood (Glorioso et al., 2006).

## *2.2. Somatostatinergic receptors in the central nervous system*

Many studies mapped the expression of individual somatostatin receptor (sst) subtypes in brain using *in situ* hybridization and immunohistochemistry and have been reviewed elsewhere (for example, see Dournaud et al., 2000, Schulz et al., 2000). Sst knock-out (KO) mice, especially the sst KO/lacZ knock-in strains (Allen et al., 2003, Strowski et al., 2003), also contributed to the precise anatomical and cellular distribution of the subtypes.

Figure 2A illustrates the major variations observed in iodinated SRIF binding between mice invalidated for each different sst. While a similar binding pattern is observed in wild-type, sst1, sst3 and sst4 KO brain, specific binding is dramatically reduced in sst2 KO brain, suggesting that sst2 is the most abundant somatostatin receptor in the murine CNS (Videau et al., 2003). Pharmacological and quantitative binding analyses did not reveal compensatory mechanisms between subtypes but did pinpoint the discrete coexpression of other subtypes together with sst2 in specific brain regions (Fig. 2B). The physiological specificity of the peptide may then be mediated by the functional interaction of given receptor isoforms, such as oligomerization mechanisms shown to modulate sst transduction *in vitro* (for a review see Olias et al., 2004).

SST2 receptor immunoreactivity is widely distributed in the brain. Since most studies were performed in rats using antibodies directed against sst2A, this isoform is presumed to be predominant in brain, but a strong expression of an alternative splicing variant sst2B has also been reported in mice and some rat tissues (Sarret et al., 1998, Schindler et al., 1999).

Light immunohistochemistry examination of sst2A distribution clearly revealed cells with a somatodendritic labeling profile in some brain areas (*ie* olfactory tubercle, central amygdala, medial septum, bed nucleus of the stria terminalis, dorsal horn of the spinal cord). In other regions (*ie* endopiriform nucleus, claustrum, hippocampal formation, deep layers of the cortex, basolateral amygdala) sst2A immunostaining revealed a homogeneous and diffuse labeling of the neuropil with no evident association with particular cell types or cellular compartments (Dournaud et al., 2000). Acute *in vivo* injection of somatostatin or sst2-preferring agonist in these areas induced a switch from the diffuse staining pattern to a somatodendritic one, resulting from sst2A receptors internalization and accumulation into the somatodendritic compartment (Csaba et al., 2002). This internalization process is mediated by the retrograde transport of the receptors through a microtubule-dependent mechanism to a *Trans*-Golgi domain before recycling, in the absence of *de novo* sst2 synthesis (Csaba et al., 2007). Agonist-induced internalization of sst2A has been useful to localize the cellular origin of diffuse staining (see Fig. 3), with respect to somatostatin afferents especially, and to



characterize the neurochemical phenotype of the receptor-expressing cells. In several regions, including the central amyloid nucleus, the BNST and the premamillary nucleus, dual immunohistochemical detection of SRIF and sst2A showed that subsets of sst2A correspond to autoreceptors (Dournaud et al., 2000).

*In vivo*, the coexistence of somatodendritic as well as diffuse sst2A staining patterns suggests that differential internalisation states do exist endogenously. Indeed, in regions exhibiting somatodendritic staining, most sst2A receptors are located intracellularly at the electron microscopic level while sst2A staining is mostly associated with neuronal membrane in diffuse staining areas, mainly extrasynaptically. Furthermore somatodendritic staining is found in regions with dense somatostatinergic innervation, while diffuse staining patterns correlate with sparse somatostatinergic innervation (Dournaud et al., 1998). This suggests that the peptide regulates quantitatively and functionally sst2A receptors (Csaba and Dournaud, 2001), as also evidenced by the global increase in sst2 binding sites in SRIF-invalidated mice (Videau et al., 2003, Cammalleri et al., 2006).

Interestingly, sst2 staining is associated to principal cells that are innervated by most SRIF interneurons in several telencephalic structures (amygdala, hippocampus, retina, neocortex, see Fig. 1). This supports the hypothesis that the peptide plays a general role in the modulation of principal cells activity and inputs, as shown for other neuropeptides (Ludwig and Leng, 2006, Bernard et al., 2006). In this case, somatostatin action is locally influenced by the availability of the receptor (*ie* internalisation state), as well as its cellular distribution (receptor close or remote from the somatostatinergic innervation, see Fig. 1). Finally, the cellular sst repertoire, through oligomerization of receptors (reviewed in Olias et al., 2004), may also differentially affect the trafficking and functional properties of involved receptors.

Contrasting with the broad distribution of sst2, sst1 immunoreactivity has only been consistently described in retina, basal ganglia and mediobasal hypothalamus. Its colocalization with somatostatin in these structures suggests a presynaptic inhibitory autoreceptor function (Thermos et al., 2006). In the arcuate nucleus of the hypothalamus, sst1 has been recently found in perikarya and dendrites, mostly intracellularly, and predominantly located at the vicinity of synaptic zones (Stroh et al., 2006).

While specific sst3 binding has been reported in various brain regions, sst3 receptors are found by immunohistochemistry specifically on neuronal cilia (Schulz et al., 2000, Berbari et al., 2007), primary structures whose functional significance is still unknown (Marshall and Nonaka, 2006).

sst4 receptor immunoreactivity is found in a restricted number of rat brain areas, mainly the olfactory bulb, the cerebral cortex and the CA1 of the hippocampus (Schreff et al., 2000). Interestingly, sst4 is expressed together with sst2 in central regions involved in learning and memory processes.

Finally, a discrete and weak sst5 signal had been detected in a few brain regions (Stroh et al., 1999), which could be associated with the GABA-ergic and cholinergic basal forebrain cells which project to the cortex and are involved in the ascending reticular activating systems regulating the sleep-waking cycle (Dournaud et al., 2000). However, central somatostatinergic networks have not been studied in sst5 KO mice (Strowski et al., 2003).

### **3. Biological roles of somatostatin**

Based on its coexistence in neurons with classical neurotransmitters, its release properties and its capacity to modulate synaptic transmission and neuronal activity, somatostatin is considered as a neuromodulatory agent in the central nervous system. Acting through sst2 and given coexpressed subtypes, the peptide leads to physiological actions mediating motor, cognitive and sensory effects.

#### *3.1. Synaptic actions of somatostatin in the CNS*

Somatostatin-containing dense-core vesicles secretion from axons terminals is calcium-dependent and occurs with high stimulation (Vezzani and Hoyer, 1999). But the dendritic localization of somatostatin suggests local release at this level, in a paracrine way (see for review Lugwig et al., 2006). As for other neuropeptides, due to a high affinity for its receptors and the absence of selective reuptake mechanisms, both factors contrasting with classical neurotransmitters, somatostatin is likely to act as a « local hormone », via volume transmission (diffusion in a three-dimensional fashion within the extracellular space). But this does not preclude a « neurotransmitter-like » role at the synapse, thereby leading to two modes of action : either somatostatin, acting on a distant « third » synaptic component, modulates glutamatergic or GABAergic transmission (neuromodulatory effect) or somatostatin evokes a response on its own postsynaptic element (neurotransmitter-like effect). In both modes of action, the temporal dynamic of somatostatin effects remains slower and longer lasting when compared with classical neurotransmitters.

The neuromodulatory effects of somatostatin are mostly presynaptic. Somatostatin inhibits presynaptically glutamate release (Lanneau et al., 2000b; Baraban et al., 2004; Grilli et al., 2003), activating potassium leak current (Baraban et al., 2004), or inhibiting voltage-dependent calcium currents (Baraban et al., 2004), via sst1 (Momiya and Zaborsky, 2006), sst2 (Grilli et al., 2003) or sst5 (Baraban et al., 2004), depending on the anatomical structure. Somatostatin also presynaptically inhibits GABA release (Leresche et al., 2000; Momiya and Zaborsky, 2006). Postsynaptically, one study reported an intracellular calcium-dependent modulation of AMPA currents mediated by sst2 activation in the hypothalamus (Peineau et al., 2003). Somatostatin also exhibits long-lasting effects on glutamatergic synapses, either depressing long-term potentiation (LTP) in the dentate gyrus/lateral perforant path, (Baraban et al., 2004) or enhancing LTP in the dentate gyrus/medial perforant path (Nakata et al., 1996). Interestingly, in sst2 KO mice, glutamatergic responses were increased in hippocampal slices (Dutar et al., 2002), suggesting that SRIF exerts an inhibitory tone on glutamatergic transmission through sst2 activation (see also Cammalleri et al., 2006). Moreover, activation of sst4 receptors, selectively expressed in the hippocampal CA1, increases hippocampal glutamatergic responses, provided that sst2 is present, suggesting that both subtypes may functionally interact (Moneta et al., 2002).

Neurotransmitter-like effects of somatostatin are mainly inhibitory and are mediated by sst2. They concern *i*) dendritic hyperpolarization, through activation of either voltage-dependent ( $I_M$ ) or voltage-independent ( $I_{K(L)}$ )  $K^+$  currents (Jiang et al., 2003; Baraban et al., 2004; Meis et al., 2005), and *ii*) inhibition of voltage-activated  $Ca^{2+}$  currents and consecutive  $Ca^{2+}$ -induced currents (Viana and Hille, 1996; Baraban et al., 2004; Galarraga et al., 2007; Bagnoli et al., this issue).

In summary, somatostatin, via presynaptic inhibition of neurotransmitter release, tends to dampen inputs on principal cells. Acting directly on postsynaptic principal cells through sst2, it hyperpolarizes the neuron away from its firing threshold and inhibits voltage-dependent calcium channels, possibly interacting with several forms of plasticity. Lastly, keeping in mind the coexistence of somatostatin with GABA in interneurons and the high stimulation required for its release, the slow but long lasting tonic inhibition induced by somatostatin release on postsynaptic neurons could complete the short- to medium-duration inhibition induced by GABA. Studies of endogenous peptide release (see Sun et al., 2003) would shed light on the functional implications of the colocalization of somatostatin with classical neurotransmitters in brain functions.

### 3.2. *Physiological roles of somatostatin systems within the brain*

Somatostatin plays a key role in the control of pituitary hormone release, most notably GH, but also TSH and, in some cases ACTH and prolactin (Epelbaum, 1986). Produced in the periventricular nucleus of the hypothalamus and released from the median eminence, somatostatin inhibits directly GH secretion and counterbalances the stimulatory effect of the GH-releasing hormone (GHRH) synthesized in the hypothalamic arcuate nucleus (see Fodor et al., 2006). In addition to this direct control of GH secretion at the pituitary level, mediated through the activation of sst2 and sst5 receptors, several studies suggest an intrahypothalamic control of GH, involving primarily sst1 and sst2 receptors. Therefore, somatostatin would on one hand inhibit GHRH neurons and thus GH secretion, and on the other hand exert a negative feedback on its own release, which thereby results in a stimulation of GHRH and GH release (Lanneau et al., 2000a, 2000b ; Zheng et al., 1997).

Sex steroids, known to regulate systemic growth at numerous physiological levels, act directly at the hypothalamic level, specifically on GHRH neuronal population since exposure to sex steroids during both the neonatal and post-pubertal periods induces gender-related differences in their number or in the expression of GHRH (for review see Chowen et al. 2004 ; Kuwahara et al., 2004). Hypothalamic somatostatin receptors expressed by these cells seem also dependent on steroids since a gender-related differences in sst1 expression had been observed in the rat arcuate nucleus, both the number and labelling density of sst1 mRNA-expressing cells being two- to threefold greater in males than in females (Zhang et al., 1999). In mice, however, the number of GHRH arcuate neurons decorated with sst2a immunoreactivity is three time more abundant in females than in males (Bouyer et al., 2006). This sexual dimorphism is dependent on testosterone impregnation (Loudes et al., unpublished data).

The synaptic actions of the peptide and the wide anatomical distribution of the sst receptors in the brain (see above) clearly indicate a role for somatostatin in neuronal functions other than neuroendocrine regulatory processes .

Early intracerebroventricular administration of the peptide in rats increased locomotor activity, while SRIF depletion induced by cysteamine resulted into learning and memory deficits (for review see Viollet et al., 2000b). More recent behavioural studies of somatostatinergic invalidated models also evidenced an impairment of motor functions in sst2-invalidated animals (Viollet et al., 2000a, Allen et al., 2003), attributed to a striatal sst2 deficit. Interestingly, null mutant mice lacking somatostatin also showed a significant

impairment in motor learning (Zeyda et al., 2001). Sst2 KO mice also showed a specific facilitation of learning in a hippocampal-dependent spatial discrimination task, while working memory was not modified in an operant learning protocol (Dutar et al., 2004; for a review of KO models phenotypes, see Hoschgeschwender, this issue, Olias et al., 2004). However, somatostatin knock-outs animals did not show major learning and memory defects as opposed to mice overexpressing cortistatin, a somatostatin-related peptide (Hoschgeschwender et al., de Lecea et al., this issue).

In the hippocampus, some somatostatin-immunoreactive neurons project to the medial septum (MS) and the diagonal band of Broca (DB). The MS-DB complex, via its cholinergic and GABA-ergic projections to the hippocampus, plays a crucial role in the genesis of the hippocampal  $\theta$  rhythm and is associated with attentional and mnemonic functions. Septal GABAergic neurons express sst2A receptors and *in vivo* injection of sst2 agonists decreases the bursting of these cells and reduces  $\theta$  power, suggesting that somatostatin modulates MS-DB rhythmic activity (Bassant et al., 2005).

Somatostatin has also analgesic effects in rodents and humans when injected centrally (Malcangio, 2003). In the spinal cord, somatostatin is restricted to the dorsal horn, in unmyelinated sensory neurons, local interneurons and axons from the brain stem. sst2A and sst1 staining are intense in this same area, with sst1 labeling the dorsal medulla as well (Dournaud et al., 2000; Schulz et al., 2000). Exogenous SRIF depresses dorsal horn neurons firing when activated by noxious heat stimulation and endogenous SRIF is released following the same stimulus. Furthermore, recent studies demonstrated that sst2A is upregulated in spinal cord neurons after noxious thermal stimulation, while pretreatment with an anti-sst2A antibody induces significant attenuation of thermal, but not mechanical, hyperalgesia (Song et al., 2002). This suggests that this particular receptor subtype is responsible for thermal nociceptive transmission in the spinal cord and that differential receptor responses can occur according to the type of noxious stimuli. However, the involvement of other receptor subtypes in the transmission of nociceptive signals cannot be excluded, since other receptors have also been detected in sensory neurons of the spinal ganglia (Schulz et al., 2000; Dournaud et al., 2000).

Somatostatin shares several functional properties with cortistatin, such as the depression of neuronal activity, and perhaps anti-inflammatory action (Cauli et al., 2004; Pinter et al., 2006, Gonzalez-Rey et al., 2006, see also De Lecea, this issue). However, several biological functions of the peptides are clearly distinct. For example, somatostatin stimulates

locomotor activity while cortistatin reduces it. In sleep control, somatostatin increases REM without affecting slow-wave sleep while cortistatin induces slow-wave sleep (Spier and de Lecea, 2000). Interestingly, and also in contrast to cortistatin, somatostatin facilitates the effects of acetylcholine on cortical excitability while cortistatin antagonizes them.

Somatostatin peptide and binding sites are transiently detected at key developmental stages in several central and sensory regions, suggesting that the peptide plays a developmental role in brain ontogenesis (Shiosaka, 1992). For example, in the cortex, cerebellum or spinal cord as well as in most sensory systems, somatostatin binding sites are detected at the level of transient neuroproliferative zones, namely the cortical plate and intermediate zone, the developing neural tube and the external granule layer of the cerebellum respectively (Leroux et al., 1995), and correspond mainly to sst2 receptors (see Fig. 4 and Viollet et al., 1997). While diverging effects of the peptide on proliferation and migration processes have been reported, somatostatin modulates the migration of cerebellar granule cells in a cortical layer-specific manner *in vitro* (Yacubova and Komuro, 2002). Nevertheless, the phenotypical analysis of adult somatostatin receptor-invalidated mice did not show evident developmental defects but more subtle physiological modifications (see Hoschgeschwender, this issue; Viollet et al., 2000b; Olias et al., 2004) suggesting that developmental compensatory mechanisms may take place.

#### **4. Physiopathological implications of central somatostatinergic systems**

Long acting sst2-preferring agonists, such as octreotide and lanreotide, are widely used for the clinical management of acromegalic patients, gastroenterological or pancreatic tumors and other gastrointestinal disorders. Modified analogs are also developed for tumour imaging and radiotherapy. Not surprisingly, therapeutic applications for neuropsychiatric diseases still need to be established. Nevertheless, changes in somatostatin and sst receptors have long been associated with dementia, epilepsy and major affective disorders (Epelbaum, 1986).

Concerning affective disorders, one of the most consistent neuropeptide alterations in depression has been a state-dependent decrease of cerebrospinal fluid somatostatin. This decrease does not appear to be specific to depression, as it has been observed in other patients with impaired cognition, such as schizophrenia, Alzheimer's dementia, drug refractory epilepsy and active multiple sclerosis (Frye et al., 2003). Somatostatin decrease in affective illness and active multiple sclerosis is state-dependent, since levels normalize with recovery

from the acute episode or treatment. In contrast, increased somatostatin levels have been reported in psychiatric illness in which cognitive processes are accelerated, as in mania, or in obsessive compulsive disorder (reviewed in Frye et al., 2003). It is noteworthy that a genome-wide expression analysis detected somatostatin as one of the eight genes displaying robust alterations which appear specific to bipolar I disorder (Nakatani et al., 2006).

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 (STEP), an enzyme which counteracts the MAPK neuroprotective pathway (Choi et al., 2007. See also Florio et al., this issue). SRIF receptors may represent potential therapeutic targets for temporal lobe epilepsy. Indeed, somatostatin is released in characteristic conditions of seizures and somatostatin and its analogues affect seizures (Buckmaster et al., 2002, Vezzani and Hoyer, 1999). However, information on the precise contribution of each somatostatin receptor on the SRIF-induced inhibition of epileptiform activity is still limited. Although the  $sst_2$  receptor is likely to mediate the anticonvulsant effects of somatostatin in rat hippocampus (Vezzani and Hoyer, 1999), recent observations in the mouse support a central role of  $sst_4$  (Moneta et al., 2002) and/or  $sst_1$  receptors (Cammalleri et al., 2004, 2006) in mediating somatostatin inhibition of epileptiform activity. In a rodent model of cortical focal ischemia,  $sst_2$  is also activated while the infarct size is significantly reduced in  $sst_2$  KO mice (Stumm et al., 2004).

In Alzheimer's disease cortical somatostatinergic deficiency correlates with the dementia score in frontal cortex (Dournaud et al., 1995) and with some indices of severity of the illness (Leake and Ferrier, 1993). Selective assays indicate that somatostatin- but not cortistatin-related peptides are involved in these deficits (Grouselle et al., 1998). The proportion of proSRIF is significantly lower in the temporal cortex of Alzheimer patients and SRIF<sub>28</sub> proportions were significantly elevated (Pierotti et al., 1986). These results suggested that overall somatostatin changes are related to a reduction in the rate of biosynthesis and/or to a change in the proteolytic processing of the precursor form to yield the bioactive peptides SRIF<sub>28</sub> and SRIF<sub>14</sub> but not through PC2 protein convertases (Winsky-Sommerer et al., 2003). Since the neuropeptide seems to specifically increase neprilysin activity thereby promoting the degradation of the amyloid  $\beta$  peptide, A $\beta$ 42, supposedly the main pathogenic factor in the disease (Saito et al., 2005), monitoring brain SRIF levels may have a therapeutical and

preventive interest. For example IGF-1 (Aguado-Llera et al., 2005) or estradiol (Aguado-Llera et al., 2007) treatments in rats partially restore SRIF parameters affected after  $\beta$ -amyloid peptide infusion.

## 5. Conclusions and perspectives

Thirty five years after its discovery, somatostatin can be considered as a « successful » neuroendocrine peptide. Long-acting agonists have been used for more than 18 years in clinics for the management of GH/IGF-1 hypersecretion and tumour size in patients with GH-secreting pituitary adenoma responsive to sst-agonist therapy (Maiza et al., 2007). Nevertheless, the wide distribution of somatostatin systems throughout nearly all brain regions suggests that they play major roles in brain functioning, whose comprehension is just at its beginning. This molecular complexity, due to the variety of receptor and peptide repertoires as well as the functional regulation by agonists and/or receptor oligomerization, suggests that the peptide may induce specific and localized cellular responses. Such targeted actions, especially on principal neurons, participate to maintain the functional and physiological integrity of brain tissue. The coexistence of interneurons expressing either somatostatin or cortistatin in some brain regions and their differing functional roles suggest that the nature of the peptide itself introduces another level of action specificity, since they may act differently on principal cells. Of the 24,000 articles referenced in PubMed on somatostatin, 6,000 also refer to brain. Therefore, one might reasonably expect that future research in this domain will be fruitful in term of translational research for neuropsychiatric diseases.



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## Figure legends

### **Figure 1: Somatostatin interneurons innervate distinct subdomains of pyramidal cells in neocortex and hippocampus.**

In neocortex as in hippocampus, each somatostatinergic interneuron type innervates two distinct domains of the dendritic tree of pyramidal cells which differ by (i) their relative distance to pyramidal cell soma, (ii) their proximity to different glutamatergic inputs (for example, Schäffer collaterals vs perforant path in CA1), (iii) the existence of close postsynaptic sst receptors on pyramidal dendrites (remote sst in the case of Martinotti/O-LM cells vs close sst in the case of Basket / O-Bi cells).

*Abbreviations* : O-LM cells: Oriens-Lacunosum Moleculare cells (hippocampus). O-Bi cells: Oriens-Bistratified cells

### **Figure 2: SRIF receptors in the murine brain**

A : [<sup>125</sup>I]-Tyr<sup>0</sup>-DTrp<sup>8</sup>-SRIF<sub>14</sub> binding in different sst invalidated mice. B : SRIF receptors association in the brain. *Abbreviations* : n.s. : non specific. Adapted from Videau et al., 2003.

### **Figure 3 : Agonist-induced internalization of sst2A receptors in layers IV-V of the neocortex.**

Local injection of the sst2-selective agonist octreotide (OCT) induces a transition from a diffuse sst2A labeling (left panel, saline injection) to a somatodendritic one (right panel, octreotide injection), allowing the localization of sst2A receptors in pyramidal cells (scale bar : 200 μm).

### **Figure 4 : sst2 *in situ* hybridization in E13 rat neural tube.**

Representative pictures showing hybridization of frontal sections of embryonic day E13.5 rat embryo (Toluidine Blue counterstained in A, inset shows the cutting plane) with <sup>33</sup>P-labeled sst2 antisense (B) and sense (C) riboprobes.

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Origin	Target	Cell characteristics	References
<b>Telencephalon</b>			
Neocortex (layer II/III, VI)	Neocortex (cortico-cortical projections)	GABA+/NPY+/NOS+	■ Tomioka 2005
Hippocampus (CA1-CA3, SO & hilus of DG)	Medial septum	GABA+ (40-80% of colocalization with CB in CA1), septal targets are GABA+, PV+ and sst2A+	■ Gulyas 2003, Bassant 2005
Hilus of DG	Contralateral DG	GABA+	■ Zappone 2001
Amygdala ( <i>lateral</i> )	Preoptic hypothalamic area	VGluT1+/NPY+/CCK+	■ Epelbaum 1994, Sosulina 2006
Amygdala ( <i>central</i> )	Amygdaloid nuclei		
	BNST	GABA+	■ Epelbaum 1994, Saha 2002, Sosulina 2006
	Parabrachial nuclei		
	NTS	Neuronal targets are sst2A+.	
BNST	Dorsal motor nucleus		
	Reticular nuclei		
	Parabrachial nuclei		■ Epelbaum 1994
	NTS		
	Dorsal motor nucleus		
Entepeduncular nucleus	Habenula		■ Epelbaum 1994
Globus pallidus	Striatum		■ Widmann 1987
<b>Diencephalon</b>			
Periventricular nucleus of the hypothalamus	Median eminence Arcuate nucleus Olfactory tubercle Lateral septum Habenula Locus caeruleus Substantia nigra	38% are CART+	■ Epelbaum 1994, Larsen 2003.
Ventral posteromedial nucleus of the thalamus	Sensory cortex		■ Mantyh 1984
<b>Mesencephalon</b>			
Pedunculopontine nucleus	Medial preoptic area		■ Giehl 1995
<b>Pons</b>			
Parabrachial nucleus	Thalamus Medial preoptic area		■ Mantyh 1984, Giehl 1995
Locus caeruleus	Medial preoptic area		■ Epelbaum 1994, Giehl 1995
<b>Medulla oblongata</b>			
NTS	Paraventricular nucleus Medial preoptic area BNST Parabrachial nuclei Nucleus ambiguus		■ Epelbaum 1994, Giehl 1995.
Lateral reticular nucleus	Medial preoptic area		■ Giehl 1995
Cuneiform nucleus	Medial preoptic area Thalamus		■ Mantyh 1984, Giehl 1995
Raphe nuclei	Medial preoptic area Periaqueductal gray Olfactory bulb		■ Epelbaum 1994, Giehl 1995, Araneda 1999
Ventrolateral medulla	NTS Spinal cord		■ Epelbaum 1994
<b>Spinal cord</b>			
Dorsal root ganglia	Dorsal horn	Primary sensory neurons. Substance P+	■ Malcangio 2003

**Table 1 : Long-projecting somatostatinergic neurons in the central nervous system (CNS).**

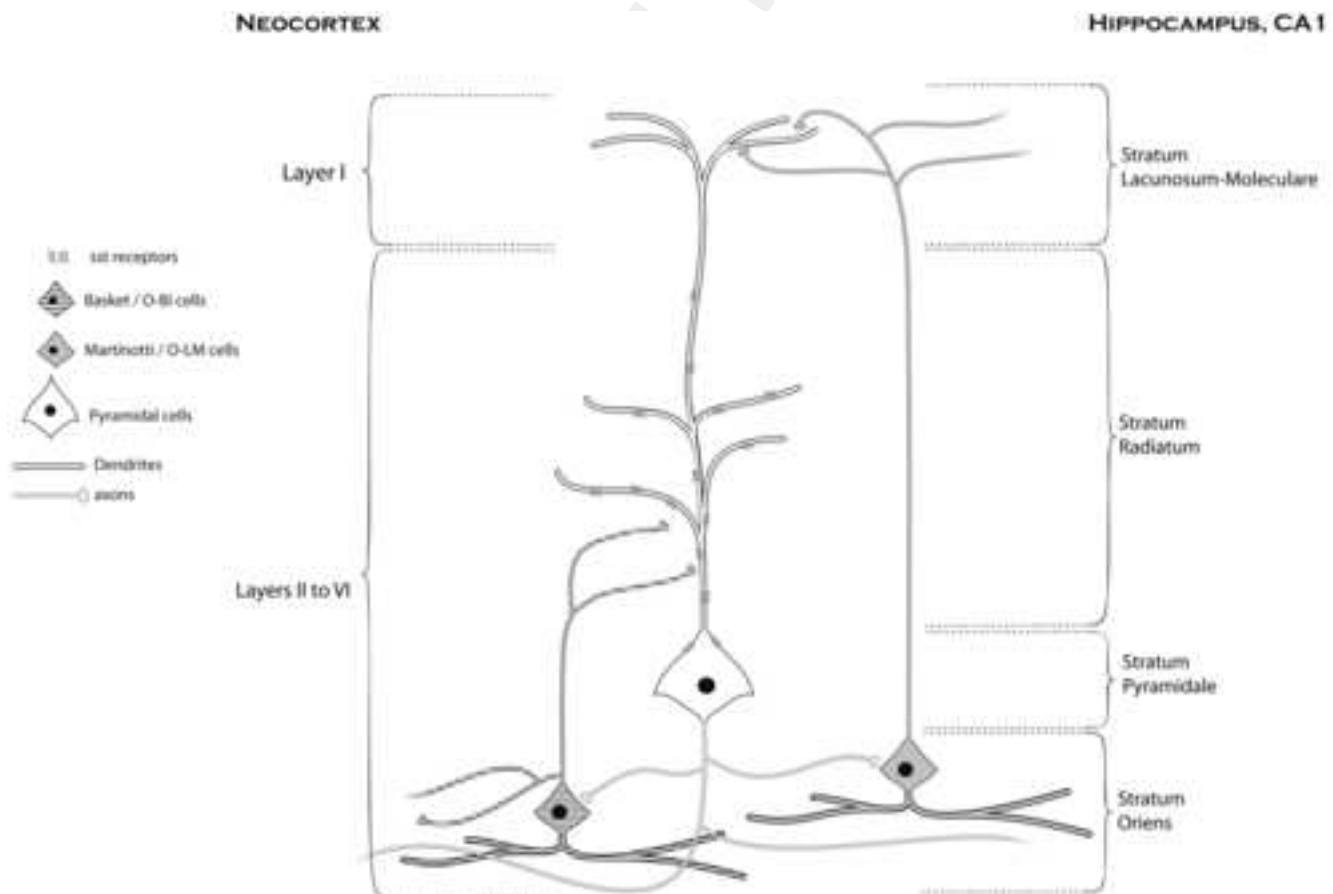
*Abbreviations* : BNST, bed nucleus of the stria terminalis ; CART, cocaine- and amphetamine-regulated transcript ; CB, calbindin ; CCK, cholecystokinin ; DG, dentate gyrus ; GABA, Gamma-aminobutyric acid ; NOS, nitric oxide synthase ; NPY, neuropeptide Y ; NTS, nucleus of the solitary tract ; PV, parvalbumin ; SO, stratum oriens ; VGluT1, vesicular glutamate transporter 1.

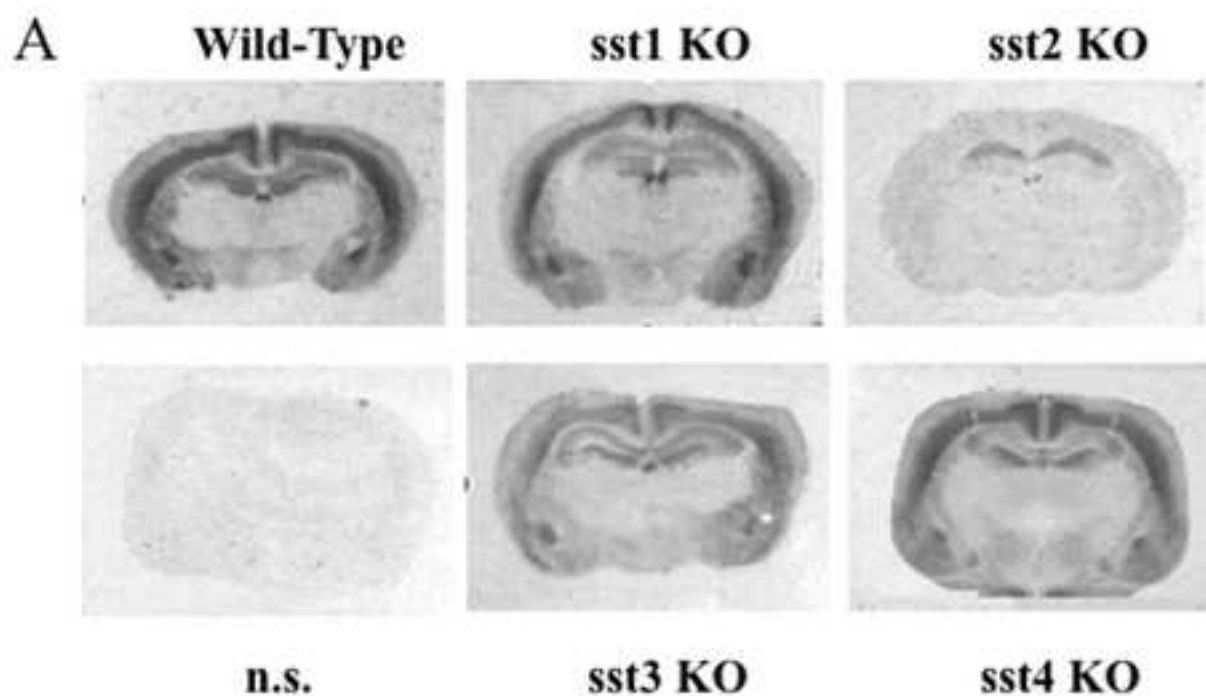
Region	Cell types	Main localization	Cellular target	References
Neocortex	Martinotti cells	Layer II-III, V, VI	Terminal branches of the apical dendrites of neocortical pyramidal cells, in layer I	Halabisky 2006, Markram 2004, Wang 2004, Ma 2006
	Nest- / small-basket cells	Layer IV, V	Soma and proximal portion of pyramidal dendrites	Kawaguchi 1998, Markram 2004, Toledo-Rodriguez 2005, Ma 2006
Hippocampus	O-LM cells HIPP cells (Density is greater in the ventral part)	SO of CA1-CA3 Hilus of the DG	Terminal branches of apical dendrites of pyramidal cells ( <i>granule cells in DG</i> ) in SLM ( <i>outer part of the molecular layer in DG</i> )	Katona 1999, Oliva 2000, Jinno 2006
	O-Bi cells	SO of CA1-CA3	Basal and intermediate portions of principal dendrites in SR and SO	Maccaferri 2000
Amygdala (lateral)	Local interneurons		Distal dendrites and spines of pyramidal cells	Sosulina 2006, Müller 2007
Neostriatum	Medium-size aspiny interneurons		GABAergic spiny projection neurons	Tepper 2004
Basal forebrain, Subst. Innom.	Local interneurons		Cell body and proximal dendrites of cholinergic neurons	Zaborzsky 2000, Momiyama 2006
Olfactory bulb	Periglomerular neurons	Glomerular layer	Apical dendrites of mitral cells	Gutierrez-Mecinas 2005

**Table 2: Recently characterized somatostatinergic interneurons in the CNS.**

*Abbreviations* : DG, dentate gyrus ; HIPP cells, hilar-perforant path associated cells ; O-Bi cells, oriens-bistratified cells ; O-LM cells, oriens-lacunosum moleculare cells; Subst. Innom. , Substantia Innominata ; SLM, stratum lacunosum moleculare ; SO, stratum oriens ; SR, stratum radiatum.

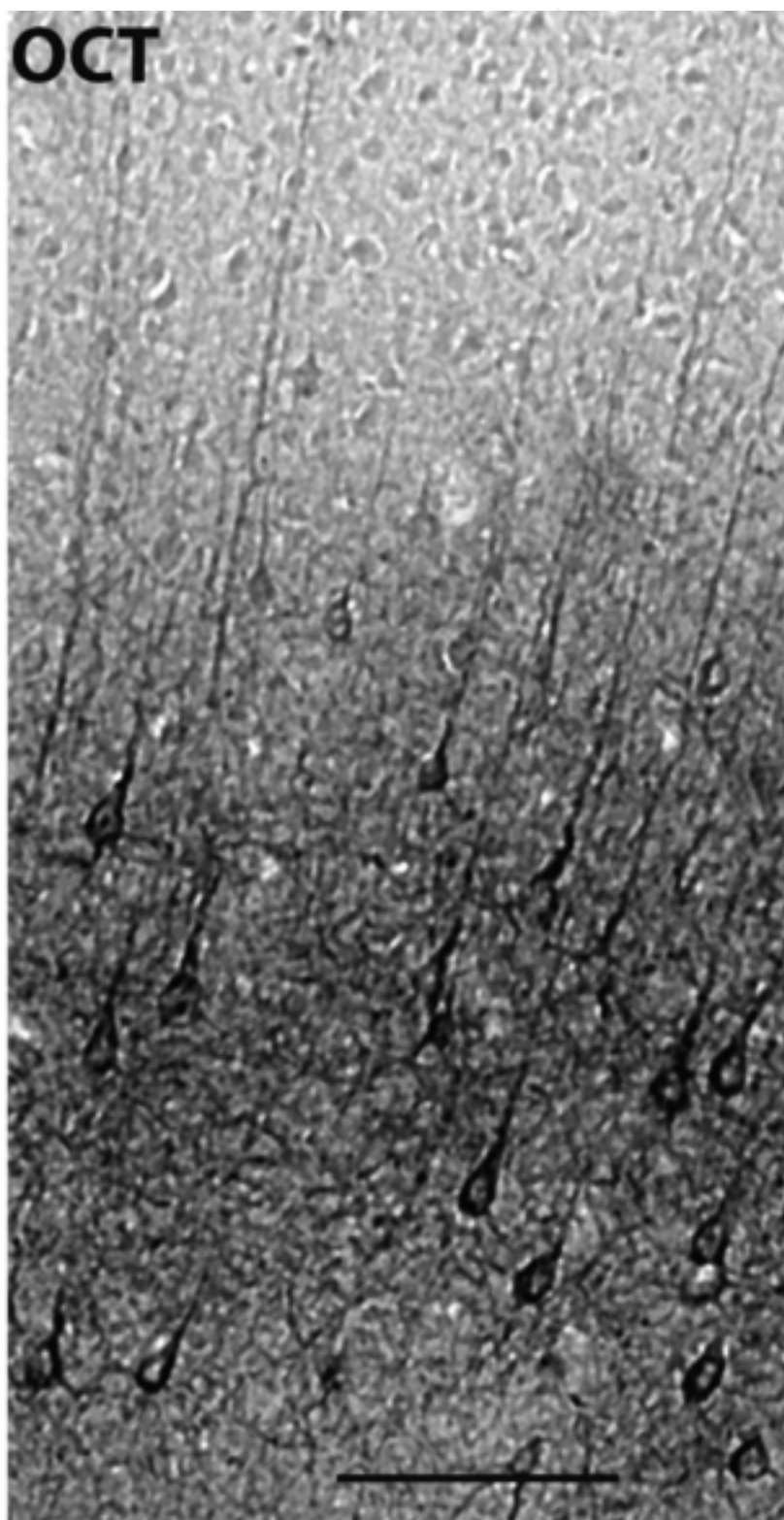
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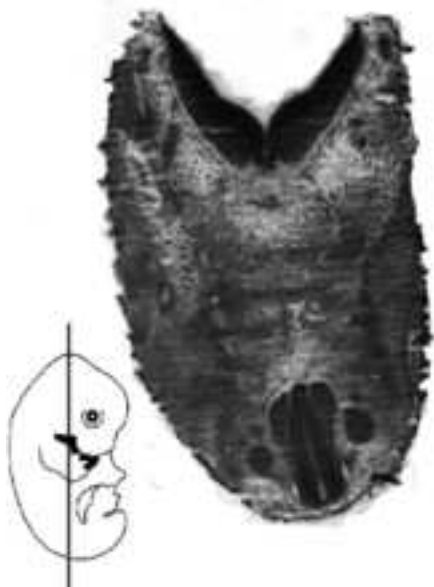


**B**

Region	main SRIF receptors
Olfactory bulb	sst2, sst3, sst4
Anterior olfactory nucleus	sst2
Neocortex	sst2, sst4
Hippocampus :	
CA1	sst2, sst4
CA3	sst2
Dentate gyrus	sst2
Amygdala	sst2
Lateral hypothalamus	sst1, sst2
Locus coeruleus	sst2



A



B



C

