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► **To cite this version:**

Stefan Jacobs, Stefan Schulz. Intracellular trafficking of somatostatin receptors. *Molecular and Cellular Endocrinology*, 2008, 286 (1-2), pp.58. 10.1016/j.mce.2007.10.005 . hal-00531954

HAL Id: hal-00531954

<https://hal.science/hal-00531954>

Submitted on 4 Nov 2010

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Accepted Manuscript

Title: Intracellular trafficking of somatostatin receptors

Authors: Stefan Jacobs, Stefan Schulz

PII: S0303-7207(07)00385-1
DOI: doi:10.1016/j.mce.2007.10.005
Reference: MCE 6724



To appear in: *Molecular and Cellular Endocrinology*

Received date: 5-7-2007
Revised date: 3-9-2007
Accepted date: 10-10-2007

Please cite this article as: Jacobs, S., Schulz, S., Intracellular trafficking of somatostatin receptors, *Molecular and Cellular Endocrinology* (2007), doi:10.1016/j.mce.2007.10.005

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**New developments in somatostatin and
cortistatin, and their receptors in physiology
and pathology**

Intracellular trafficking of somatostatin receptors

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Key Words: Somatostatin receptors, receptor internalization, endosomal sorting, receptor recycling.

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Abstract

The somatostatin receptor subtypes 1 - 5 (sst₁-sst₅) exhibit different intracellular trafficking and endosomal sorting after agonist exposure. The internalization of the somatostatin receptor subtypes sst₂, sst₃ and sst₅ occurs to a much higher extent after somatostatin exposure than of sst₁ or sst₄. After endocytosis, sst₂ and sst₅ recycle to the plasma membrane, whereas sst₃ is predominantly down-regulated. This review will focus on the molecular mechanisms of the differential intracellular trafficking of sst₂, sst₃ and sst₅, and discusses our current knowledge on somatostatin receptor interacting proteins.

1. Introduction

The biological actions of somatostatin are mediated by six G protein-coupled somatostatin receptors encoded by five different genes, named sst_1 through sst_5 . The sst_2 somatostatin receptor exists in two splice variants sst_{2A} and sst_{2B} with a different carboxyl terminus. The somatostatin receptors are expressed in neuronal as well as in non-neuronal tissues and tumors and have complex overlapping patterns of expression (Patel, 1999; Schulz et al., 2000).

Somatostatin is a regulatory peptide that exerts a broad spectrum of actions in neurotransmission and hormone secretion from anterior pituitary, pancreas and gastrointestinal tract (Schonbrunn, 2001; Schonbrunn, 2004; Olias et al., 2004). Moreover, somatostatin has been shown to inhibit secretion and growth in a number of neuroendocrine tumors (Reubi, 1997).

Due to the differential expression of somatostatin receptors in tumors, the comparison of their ability to undergo agonist-induced desensitization and internalization may provide important clues for the clinical use of somatostatin analogs (Hofland and Lamberts, 2003; Hofland et al., 2003; Reubi, 2003; Bernard et al., 2004; Kwekkeboom et al., 2005; Cescato et al., 2006; Gola et al., 2006).

Not all somatostatin receptors internalize equally after agonist binding (Csaba and Dournaud, 2001; Olias et al., 2004). Sst_2 , sst_3 and sst_5 are internalized to a much higher extent than sst_1 or sst_4 after stimulation. This review will therefore focus on the different intracellular trafficking and endosomal sorting of sst_2 , sst_3 and sst_5 (Fig. 1).

2. Somatostatin receptor 2 subtypes (ss_{2A} and ss_{2B})

The ss_2 receptor is the most widely distributed somatostatin receptor subtype in normal tissues and tumors (Liu et al., 2005). Because of the broad expression and the high binding affinity to the stable somatostatin analog octreotide, ss_2 is the best investigated somatostatin receptor.

Desensitization and internalization are not induced by ss_2 antagonists (Cescato et al., 2006), but there is a lot of data on agonist-induced desensitization and/or internalization of the ss_2 subtypes as assessed in several cell lines and tissues (Boudin et al., 2000; Csaba et al., 2001; Csaba and Dournaud, 2001; Csaba et al., 2002; Liu et al., 2005).

Both ss_2 splicing isoforms are rapidly desensitized and internalized after agonist-mediated phosphorylation (Vanetti et al., 1993; Hipkin et al., 1997). Investigations of the state of phosphorylation from the human ss_{2A} in neuroendocrine tumors showed that the receptor from a somatostatinoma was completely phosphorylated. In contrast, only unphosphorylated ss_{2A} was present in tumors that did not express somatostatin mRNA. Further immunocytochemical localization studies showed that the phosphorylated receptor was mostly intracellular, whereas the unphosphorylated receptor was localized at the cell surface (Liu et al., 2003).

In ss_{2A} overexpressing GH4C1 cells, the desensitization and phosphorylation of the ss_{2A} seemed not to be dependent on protein kinase C (PKC) (Hipkin et al., 1997). Indeed, an incubation of cells with phorbol 12-myristate 13-acetate did not increase the phosphorylation and internalization of ss_{2A} (Hipkin et al., 2000). Furthermore, the phosphorylation of the endogenous ss_2 in AR42J rat pancreatic acinar cells after exposure with somatostatin or the heterologous hormones bombesin and cholecystokinin were not PKC-dependent, too. This was confirmed by the observation of phosphorylation and internalization of ss_2 in the presence of a PKC inhibitor (Elberg et al., 2002).

Even though the phosphorylation sites are located in the third intracellular loop and in the C terminal tail of the receptor, a truncated ss_{2A} with lacking the last 20 amino acids of the C-

terminus was shown to undergo agonist-independent constitutive internalization without being phosphorylated. Moreover, a truncated form of the receptor lacking the last 44 amino acids from the C-terminus was efficiently internalized after agonist activation without being phosphorylated (Schwartzkop et al., 1999). Seemingly, phosphorylation of the C-terminal domain of sst_{2A} is not necessary for receptor internalization.

Cescato et al. found that a high binding affinity of the agonist is a prerequisite for triggering sst_2 internalization. The sst_5 -selective agonist L-817/818 with a low affinity to sst_2 is not able to cause internalization of the sst_2 , whereas ligands with high affinity like BIM-23244 induce a high internalization. Besides the binding affinity of the agonist, factors with cell-specific effects play an important role in the degree of receptor internalization. After receptor activation, sst_2 is rapidly phosphorylated by G-protein-coupled-receptor-kinases (GRKs) (Hipkin et al., 1997; Tulipano et al., 2004). Receptor phosphorylation is followed by recruitment of β -arrestin to the receptor (Liu et al., 2005), which both form a stable complex and are internalized together into the same endocytotic vesicles (Tulipano et al., 2004; Liu et al., 2005). Thus, the concentration of different β -arrestins as well as GRK-subtypes affect the extent of receptor internalization (Menard et al., 1997).

With mutants of rat sst_{2A} lacking either 10, 15, or 20 amino acids from the C-terminus and a mutant in which Thr353,355,356 were replaced by alanine residues, it was demonstrated that the cluster of Thr353,355,356 is crucial for β -arrestin binding and may represent the primary site for GRK-2-mediated phosphorylation (Tulipano et al., 2004). Although β -arrestin is endocytosed with the receptor after somatostatin stimulation, it was proposed to play a role in desensitization rather than receptor internalization because expression of a dominant-negative β -arrestin failed to inhibit sst_2 endocytosis (Brasselet et al., 2002). The sst_{2B} may resemble a truncated mutant of sst_{2A} lacking the cluster of threonine residues in position 353–356. Interestingly, in CHO-K1-transfected cells, mouse sst_{2B} mediated a more efficient inhibition of adenylyl cyclase (AC) and appeared to be more resistant to agonist-induced desensitization than the longer isoform (Vanetti et al., 1993).

Several studies suggest that sst_{2A} is efficiently recycled to the cell surface and does not enter

any degradative pathway. Nearly the entire pool of internalized rat sst_{2A} recycles to the plasma membrane during a 40 min-incubation in the absence of somatostatin. Most GPCRs in the brain enter a rapid recycling pathway through early/recycling endosomes. Likewise, a high degree of sst_{2A} was found after *in vivo* agonist induced internalization in early/recycling endosomal compartments after clathrin-dependent endocytosis (Stumm et al., 2004; Tsao and von Zastrow, 2000; Csaba et al., 2001). Before recycling to the plasma membrane, sst_2 seems to be selectively transported back to a trans-Golgi domain (Csaba and Dournaud, 2007). This alternative postendocytotic recycling route could be necessary for sst_2 to interact with chaperones or escort proteins for proper confirmation and delivery to the plasma membrane (Duvernay et al., 2005). Recent studies suggest that amphiphysin IIb is involved in receptor targeting from the trans-Golgi network to the plasma membrane (Sarret et al., 2004).

The C-terminus of sst_2 contains a consensus sequence for recognition of PDZ domains (Kreienkamp et al., 2000). Kreienkamp et al. detected and cloned the sst_2 interacting proteins cortactin-binding protein 1 (CortBP1) and the postsynaptic protein SSTRIP/Shank1, which bind specifically to the PDZ domain of sst_2 and seem to be responsible for the subcellular location of sst_2 in neurons. Indeed, CortBP1 is relocalized to the plasma membrane if sst_2 is co-transfected (Zitzer et al., 1999a). CortBP1 probably causes the anchoring of sst_2 in nerve terminals, where sst_2 functions as a regulator for transmitter release. SSTRIP/Shank1 is an important structural protein in the postsynaptic density and anchors sst_2 to the postsynapse (Zitzer et al., 1999b).

3. Somatostatin receptor subtype 3 (sst₃)

Rat sst₃ inhibits forskolin-stimulated cAMP levels in sst₃-overexpressing HEK293 and rat insulinoma cells (RIN) after somatostatin stimulation (Roosterman et al., 1997; Roth et al., 1997a). The rat sst₃ contains several putative phosphate acceptor sites, which are phosphorylated after agonist treatment. Four hydroxyl amino acid residues in the C-terminus (Ser341, Ser346, Ser351, Thr357) have been identified as primary sites of agonist-dependent receptor phosphorylation. These four residues are also required for agonist-induced receptor desensitization and internalization (Roth et al., 1997a), however, the phosphorylation of these sites was largely independent of GRK-2 (Tulipano et al., 2004).

As for sst_{2A}, human and rat sst₃ internalize efficiently after agonist stimulation through a clathrin-dependent mediated pathway (Hukovic et al., 1996; Roosterman et al., 1997; Roth et al., 1997a; Roth et al., 1997b; Kreuzer et al., 2001). Rat sst₃ recruits β -arrestin-2 with a higher affinity than β -arrestin-1. The β -arrestin-sst₃ complex dissociates after prolonged agonist exposure and β -arrestin is redistributed to the cytoplasm, so that it appears that β -arrestin and the receptor are not endocytosed together.

Without stimulation, sst₃ is almost exclusively located at the plasma membrane. After 30 min treatment with an agonist, the receptor is internalized. In contrast to sst_{2A}, after agonist withdrawal only a small amount of sst₃ is recycled to the cell surface, whereas the majority of the receptor is clustered in relatively large intracellular vesicles. Colocalization studies showed that sst₃ was initially located in transferrin-positive vesicles (early/recycling endosomes) like sst_{2A}, but was then sorted to vesicles that did not contain transferrin and therefore were no longer included into the recycling pathway. Moreover, sst₃ undergoes considerable down-regulation during prolonged agonist exposure. The degradation after agonist stimulation is blocked by the lysosomal inhibitor chloroquine and the proteasomal inhibitor MG132. The different endosomal sorting of sst₂ and sst₃ could be due to different ubiquitination. Indeed it could be shown that after stimulation many ubiquitine monomers were linked to sst₃ and not to sst_{2A} (Tulipano et al., 2004).

4. Somatostatin receptor subtype 5 (sst₅)

Sst₅ has a greater affinity to somatostatin-28 than sst_{2A} or sst₃, which have a higher affinity to somatostatin-14. Furthermore sst₅ differs from sst_{2A} and sst₃ in its cellular localization. Sst₅ appears to be predominantly located in intracellular components in overexpressing cells even without agonist treatment (Roosterman et al., 1997; Stroh et al., 2000; Sarret et al., 2004). After stimulation, a large amount of intracellular receptors is recruited to the cell surface (Roosterman et al., 1997; Stroh et al., 2000). The cellular distribution and post-stimulus reaction of the receptor was also shown in corticotropin adenoma cells with endogenous sst₅-expression by Sarret et al..

The human sst₅ desensitizes in CHO-transfected cells in response to agonist (Wilkinson et al., 1997; Hukovic et al., 1998). The lack of a cluster of phosphorylation sites seems to be responsible for a low stability of interaction with β -arrestins. Nevertheless, sst₅ efficiently internalizes after treatment with the native agonists somatostatin-28 and somatostatin-14, whereas high-affinity synthetic sst₅ agonists did not cause rapid internalization of sst₅ in transfected HEK293 cells (Cescato et al., 2006). The differential effects of sst₅ agonist on signaling and internalization suggest a lower efficacy of sst₅ compared with sst₂ receptors. However, confocal microscopy studies indicate that somatostatin was efficiently internalized into the cell, whereas the receptor remained associated with the cell surface. The receptor availability at the membrane during agonist treatment shows a high recycling rate or mobilization from an intracellular receptor pool to the cell surface (Stroh et al., 2000).

Wente et al. identified two PDZ-domain containing proteins PIST and PDZK1, which interact with the C-terminus of sst₅ and seem to regulate its intracellular transport (Wente et al., 2005). Remarkably, all sst subtypes have a PDZ-binding motif in the C-terminal tail (Wente et al., 2005). PIST is a Golgi apparatus associated protein and colocalizes with sst₅ in mouse pituitary AtT-20 cells. A truncated sst₅ mutant lacking the last 12 amino acids of the C-terminus did not colocalize with PIST, suggesting that the C-terminal PDZ motif is crucial for the intracellular localization of sst₅. Moreover, the loss of the PDZ motif inhibits sst₅ receptor

recycling, but did not interfere with the internalization after agonist treatment.

5. Concluding remarks

The differential intracellular trafficking of somatostatin receptors is likely to be involved in the regulation of long-term responsiveness of individual target cells to stable somatostatin analogs. The sst_2 receptor appears to be an ideal pharmacological target because the lack of detectable down-regulation may enable target cells to retain their responsiveness during prolonged agonist exposure. In addition, the rapid internalization and recycling of sst_2 may allow the accumulation of considerable amounts of radiolabeled somatostatin analogs in target cells. In contrast, due to its rapid down-regulation, the sst_3 receptor appears to be a less favourable pharmacological target. At present only limited knowledge exists regarding specific interacting proteins which modulate the differential intracellular trafficking of somatostatin receptors.

Figure legends

Figure 1. Somatostatin receptors undergo agonist induced phosphorylation and recruitment of β -arrestins. This process is rapidly followed by endocytosis of activated receptor/arrestin complexes and their subsequent trafficking toward various intracellular compartments leading to either the recycling of the receptors to the cell surface or to their concomitant degradation in lysosomes. Nearly the entire pool of activated sst2 and sst5 enters the recycling pathway through early/recycling endosomes. Amphysins and PDZ-domain containing proteins may be involved in the receptor localization during recycling. In contrast the majority of sst3 is sorted from early/recycling endosomes to lysosomes and sustains a down-regulation.

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