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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 (sst<sub>1</sub>-sst<sub>5</sub>) exhibit different intracellular trafficking and endosomal sorting after agonist exposure. The internalization of the somatostatin receptor subtypes sst<sub>2</sub>, sst<sub>3</sub> and sst<sub>5</sub> occurs to a much higher extent after somatostatin exposure than of sst<sub>1</sub> or sst<sub>4</sub>. After endocytosis, sst<sub>2</sub> and sst<sub>5</sub> recycle to the plasma membrane, whereas sst<sub>3</sub> is predominantly down-regulated. This review will focus on the molecular mechanisms of the differential intracellular trafficking of sst<sub>2</sub>, sst<sub>3</sub> and sst<sub>5</sub>, 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 (sst<sub>2A</sub> and sst<sub>2B</sub>)

The sst<sub>2</sub> 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, sst<sub>2</sub> is the best investigated somatostatin receptor.

Desensitization and internalization are not induced by sst<sub>2</sub> antagonists (Cescato et al., 2006), but there is a lot of data on agonist-induced desensitization and/or internalization of the sst<sub>2</sub> 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 sst<sub>2</sub> 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 sst<sub>2A</sub> in neuroendocrine tumors showed that the receptor from a somatostatinoma was completely phosphorylated. In contrast, only unphosphorylated sst<sub>2A</sub> 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 sst<sub>2A</sub> overexpressing GH4C1 cells, the desensitization and phosphorylation of the sst<sub>2A</sub> 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 sst<sub>2A</sub> (Hipkin et al., 2000). Furthermore, the phosphorylation of the endogenous sst<sub>2</sub> 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 sst<sub>2</sub> 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 sst<sub>2A</sub> 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  $\text{sst}_{2A}$  is not necessary for receptor internalization.

Cescato et al. found that a high binding affinity of the agonist is a prerequisite for triggering  $\text{sst}_2$  internalization. The  $\text{sst}_5$ -selective agonist L-817/818 with a low affinity to  $\text{sst}_2$  is not able to cause internalization of the  $\text{sst}_2$ , 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,  $\text{sst}_2$  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  $\beta$ -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  $\beta$ -arrestins as well as GRK-subtypes affect the extent of receptor internalization (Menard et al., 1997).

With mutants of rat  $\text{sst}_{2A}$  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  $\beta$ -arrestin binding and may represent the primary site for GRK-2-mediated phosphorylation (Tulipano et al., 2004). Although  $\beta$ -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  $\beta$ -arrestin failed to inhibit  $\text{sst}_2$  endocytosis (Brasselet et al., 2002). The  $\text{sst}_{2B}$  may resemble a truncated mutant of  $\text{sst}_{2A}$  lacking the cluster of threonine residues in position 353–356. Interestingly, in CHO-K1-transfected cells, mouse  $\text{sst}_{2B}$  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  $\text{sst}_{2A}$  is efficiently recycled to the cell surface and does not enter



any degradative pathway. Nearly the entire pool of internalized rat sst<sub>2A</sub> 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<sub>2A</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> contains a consensus sequence for recognition of PDZ domains (Kreienkamp et al., 2000). Kreienkamp et al. detected and cloned the sst<sub>2</sub> interacting proteins cortactin-binding protein 1 (CortBP1) and the postsynaptic protein SSTRIP/Shank1, which bind specifically to the PDZ domain of sst<sub>2</sub> and seem to be responsible for the subcellular location of sst<sub>2</sub> in neurons. Indeed, CortBP1 is relocalized to the plasma membrane if sst<sub>2</sub> is co-transfected (Zitzer et al., 1999a). CortBP1 probably causes the anchoring of sst<sub>2</sub> in nerve terminals, where sst<sub>2</sub> functions as a regulator for transmitter release. SSTRIP/Shank1 is an important structural protein in the postsynaptic density and anchors sst<sub>2</sub> to the postsynapse (Zitzer et al., 1999b).

### 3. Somatostatin receptor subtype 3 (sst<sub>3</sub>)

Rat sst<sub>3</sub> inhibits forskolin-stimulated cAMP levels in sst<sub>3</sub>-overexpressing HEK293 and rat insulinoma cells (RIN) after somatostatin stimulation (Roosterman et al., 1997; Roth et al., 1997a). The rat sst<sub>3</sub> 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<sub>2A</sub>, human and rat sst<sub>3</sub> 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 sst<sub>3</sub> recruits  $\beta$ -arrestin-2 with a higher affinity than  $\beta$ -arrestin-1. The  $\beta$ -arrestin-sst<sub>3</sub> complex dissociates after prolonged agonist exposure and  $\beta$ -arrestin is redistributed to the cytoplasm, so that it appears that  $\beta$ -arrestin and the receptor are not endocytosed together.

Without stimulation, sst<sub>3</sub> is almost exclusively located at the plasma membrane. After 30 min treatment with an agonist, the receptor is internalized. In contrast to sst<sub>2A</sub>, after agonist withdrawal only a small amount of sst<sub>3</sub> is recycled to the cell surface, whereas the majority of the receptor is clustered in relatively large intracellular vesicles. Colocalization studies showed that sst<sub>3</sub> was initially located in transferrin-positive vesicles (early/recycling endosomes) like sst<sub>2A</sub>, but was then sorted to vesicles that did not contain transferrin and therefore were no longer included into the recycling pathway. Moreover, sst<sub>3</sub> 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 sst<sub>2</sub> and sst<sub>3</sub> could be due to different ubiquitination. Indeed it could be shown that after stimulation many ubiquitine monomers were linked to sst<sub>3</sub> and not to sst<sub>2A</sub> (Tulipano et al., 2004).

#### 4. Somatostatin receptor subtype 5 (sst<sub>5</sub>)

Sst<sub>5</sub> has a greater affinity to somatostatin-28 than sst<sub>2A</sub> or sst<sub>3</sub>, which have a higher affinity to somatostatin-14. Furthermore sst<sub>5</sub> differs from sst<sub>2A</sub> and sst<sub>3</sub> in its cellular localization. Sst<sub>5</sub> 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 corticotropic adenoma cells with endogenous sst<sub>5</sub>-expression by Sarret et al..

The human sst<sub>5</sub> 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  $\beta$ -arrestins. Nevertheless, sst<sub>5</sub> efficiently internalizes after treatment with the native agonists somatostatin-28 and somatostatin-14, whereas high-affinity synthetic sst<sub>5</sub> agonists did not cause rapid internalization of sst<sub>5</sub> in transfected HEK293 cells (Cescato et al., 2006). The differential effects of sst<sub>5</sub> agonist on signaling and internalization suggest a lower efficacy of sst<sub>5</sub> compared with sst<sub>2</sub> 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 sst<sub>5</sub> 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 sst<sub>5</sub> in mouse pituitary AtT-20 cells. A truncated sst<sub>5</sub> 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 sst<sub>5</sub>. Moreover, the loss of the PDZ motif inhibits sst<sub>5</sub> 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  $\beta$ -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.

## References

- Bernard B., Capello A., van Hagen M., Breeman W., Srinivasan A., Schmidt M., Erion J., van Gasteren A., Krenning E., de Jong M., 2004. Radiolabeled RGD-DTPA-Tyr3-octreotate for receptor-targeted radionuclide therapy. *Cancer Biother Radiopharm* 19, 173-180.
- Boudin H., Sarret P., Mazella J., Schonbrunn A., Beaudet A., 2000. Somatostatin-induced regulation of SST(2A) receptor expression and cell surface availability in central neurons: role of receptor internalization. *J Neurosci* 20, 5932-5939.
- Brasselet S., Guillen S., Vincent J.P., Mazella J., 2002. Beta-arrestin is involved in the desensitization but not in the internalization of the somatostatin receptor 2A expressed in CHO cells. *FEBS Lett* 516, 124-128.
- Cescato R., Schulz S., Waser B., Eltschinger V., Rivier J.E., Wester H.J., Culler M., Ginj M., Liu Q., Schonbrunn A., Reubi J.C., 2006. Internalization of sst2, sst3, and sst5 receptors: effects of somatostatin agonists and antagonists. *J Nucl Med* 47, 502-511.
- Csaba Z., Dournaud P., 2001. Cellular biology of somatostatin receptors. *Neuropeptides* 35, 1-23.
- Csaba Z., Dournaud P., 2007. Activated somatostatin type 2 receptors traffic in vivo from dendrites to the trans-golgi network. *Ideggyogy Sz* 60, 136-139.
- Csaba Z., Simon A., Helboe L., Epelbaum J., Dournaud P., 2002. Neurochemical characterization of receptor-expressing cell populations by in vivo agonist-induced internalization: insights from the somatostatin sst2A receptor. *J Comp Neurol* 454, 192-199.
- Csaba Z., Bernard V., Helboe L., Bluet-Pajot M.T., Bloch B., Epelbaum J., Dournaud P., 2001. In vivo internalization of the somatostatin sst2A receptor in rat brain: evidence for translocation of cell-surface receptors into the endosomal recycling pathway. *Mol Cell Neurosci* 17, 646-661.
- Duvernay M.T., Filipeanu C.M., Wu G., 2005. The regulatory mechanisms of export trafficking of G protein-coupled receptors. *Cell Signal* 17, 1457-1465.
- Elberg G., Hipkin R.W., Schonbrunn A., 2002. Homologous and heterologous regulation of somatostatin receptor 2. *Mol Endocrinol* 16, 2502-2514.
- Gola M., Bonadonna S., Mazziotti G., Amato G., Giustina A., 2006. Resistance to somatostatin analogs in acromegaly: an evolving concept? *J Endocrinol Invest* 29, 86-93.
- Hipkin R.W., Wang Y., Schonbrunn A., 2000. Protein kinase C activation stimulates the phosphorylation and internalization of the sst2A somatostatin receptor. *J Biol Chem* 275, 5591-5599.

- Hipkin R.W., Friedman J., Clark R.B., Eppler C.M., Schonbrunn A., 1997. Agonist-induced desensitization, internalization, and phosphorylation of the sst2A somatostatin receptor. *J Biol Chem* 272, 13869-13876.
- Hofland L.J., Lamberts S.W., 2003. The pathophysiological consequences of somatostatin receptor internalization and resistance. *Endocr Rev* 24, 28-47.
- Hofland L.J., Lamberts S.W., van Hagen P.M., Reubi J.C., Schaeffer J., Waaijers M., van Koetsveld P.M., Srinivasan A., Krenning E.P., Breeman W.A., 2003. Crucial role for somatostatin receptor subtype 2 in determining the uptake of [<sup>111</sup>In-DTPA-D-Phe1]octreotide in somatostatin receptor-positive organs. *J Nucl Med* 44, 1315-1321.
- Hukovic N., Panetta R., Kumar U., Patel Y.C., 1996. Agonist-dependent regulation of cloned human somatostatin receptor types 1-5 (hSSTR1-5): subtype selective internalization or upregulation. *Endocrinology* 137, 4046-4049.
- Hukovic N., Panetta R., Kumar U., Rocheville M., Patel Y.C., 1998. The cytoplasmic tail of the human somatostatin receptor type 5 is crucial for interaction with adenylyl cyclase and in mediating desensitization and internalization. *J Biol Chem* 273, 21416-21422.
- Kreienkamp H.J., Zitzer H., Richter D., 2000. Identification of proteins interacting with the rat somatostatin receptor subtype 2. *J Physiol Paris* 94, 193-198.
- Kreuzer O.J., Krisch B., Dery O., Bunnett N.W., Meyerhof W., 2001. Agonist-mediated endocytosis of rat somatostatin receptor subtype 3 involves beta-arrestin and clathrin coated vesicles. *J Neuroendocrinol* 13, 279-287.
- Kwekkeboom D.J., Mueller-Brand J., Paganelli G., Anthony L.B., Pauwels S., Kvols L.K., O'Dorisio T M., Valkema R., Bodei L., Chinol M., Maecke H.R., Krenning E.P., 2005. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. *J Nucl Med* 46 Suppl 1, 62S-66S.
- Liu Q., Reubi J.C., Wang Y., Knoll B.J., Schonbrunn A., 2003. In vivo phosphorylation of the somatostatin 2A receptor in human tumors. *J Clin Endocrinol Metab* 88, 6073-6079.
- Liu Q., Cescato R., Dewi D.A., Rivier J., Reubi J.C., Schonbrunn A., 2005. Receptor signaling and endocytosis are differentially regulated by somatostatin analogs. *Mol Pharmacol* 68, 90-101.
- Menard L., Ferguson S.S., Zhang J., Lin F.T., Lefkowitz R.J., Caron M.G., Barak L.S., 1997. Synergistic regulation of beta2-adrenergic receptor sequestration: intracellular complement of beta-adrenergic receptor kinase and beta-arrestin determine kinetics of internalization. *Mol Pharmacol* 51, 800-808.
- Olias G., Viollet C., Kusserow H., Epelbaum J., Meyerhof W., 2004. Regulation and function of somatostatin receptors. *J Neurochem* 89, 1057-1091.
- Patel Y.C., 1999. Somatostatin and its receptor family. *Front Neuroendocrinol* 20, 157-198.

- Reubi J.C., 1997. Regulatory peptide receptors as molecular targets for cancer diagnosis and therapy. *Q J Nucl Med* 41, 63-70.
- Reubi J.C., 2003. Peptide receptors as molecular targets for cancer diagnosis and therapy. *Endocr Rev* 24, 389-427.
- Roosterman D., Roth A., Kreienkamp H.J., Richter D., Meyerhof W., 1997. Distinct agonist-mediated endocytosis of cloned rat somatostatin receptor subtypes expressed in insulinoma cells. *J Neuroendocrinol* 9, 741-751.
- Roth A., Kreienkamp H.J., Meyerhof W., Richter D., 1997a. Phosphorylation of four amino acid residues in the carboxyl terminus of the rat somatostatin receptor subtype 3 is crucial for its desensitization and internalization. *J Biol Chem* 272, 23769-23774.
- Roth A., Kreienkamp H.J., Nehring R.B., Roosterman D., Meyerhof W., Richter D., 1997b. Endocytosis of the rat somatostatin receptors: subtype discrimination, ligand specificity, and delineation of carboxy-terminal positive and negative sequence motifs. *DNA Cell Biol* 16, 111-119.
- Sarret P., Esdaile M.J., McPherson P.S., Schonbrunn A., Kreienkamp H.J., Beaudet A., 2004. Role of amphiphysin II in somatostatin receptor trafficking in neuroendocrine cells. *J Biol Chem* 279, 8029-8037.
- Schonbrunn A., 2001. Somatostatin. *Endocrinology* (Degroot L.J. and Jameson J.L. eds) WB Saunders Co, Philadelphia 427-437.
- Schonbrunn A., 2004. Somatostatin receptors. *Encyclopedia of Biological Chemistry* (Lennarz W.J. and Lane M.D. eds) Elsevier, Oxford 55-60.
- Schulz S., Handel M., Schreff M., Schmidt H., Holtt V., 2000. Localization of five somatostatin receptors in the rat central nervous system using subtype-specific antibodies. *J Physiol Paris* 94, 259-264.
- Schwartzkop C.P., Kreienkamp H.J., Richter D., 1999. Agonist-independent internalization and activity of a C-terminally truncated somatostatin receptor subtype 2 (delta349). *J Neurochem* 72, 1275-1282.
- Stroh T., Jackson A.C., Sarret P., Dal Farra C., Vincent J.P., Kreienkamp H.J., Mazella J., Beaudet A., 2000. Intracellular dynamics of sst5 receptors in transfected COS-7 cells: maintenance of cell surface receptors during ligand-induced endocytosis. *Endocrinology* 141, 354-365.
- Stumm R.K., Zhou C., Schulz S., Endres M., Kronenberg G., Allen J.P., Tulipano G., Holtt V., 2004. Somatostatin receptor 2 is activated in cortical neurons and contributes to neurodegeneration after focal ischemia. *J Neurosci* 24, 11404-11415.
- Tsao P.I., von Zastrow M., 2000. Type-specific sorting of G protein-coupled receptors after endocytosis. *J Biol Chem* 275, 11130-11140.



- Tulipano G., Stumm R., Pfeiffer M., Kreienkamp H.J., Holtt V., Schulz S., 2004. Differential beta-arrestin trafficking and endosomal sorting of somatostatin receptor subtypes. *J Biol Chem* 279, 21374-21382.
- Vanetti M., Vogt G., Holtt V., 1993. The two isoforms of the mouse somatostatin receptor (mSSTR2A and mSSTR2B) differ in coupling efficiency to adenylate cyclase and in agonist-induced receptor desensitization. *FEBS Lett* 331, 260-266.
- Wente W., Stroh T., Beaudet A., Richter D., Kreienkamp H.J., 2005. Interactions with PDZ domain proteins PIST/GOPC and PDZK1 regulate intracellular sorting of the somatostatin receptor subtype 5. *J Biol Chem* 280, 32419-32425.
- Wilkinson G.F., Feniuk W., Humphrey P.P., 1997. Characterization of human recombinant somatostatin sst5 receptors mediating activation of phosphoinositide metabolism. *Br J Pharmacol* 121, 91-96.
- Zitzer H., Richter D., Kreienkamp H.J., 1999a. Agonist-dependent interaction of the rat somatostatin receptor subtype 2 with cortactin-binding protein 1. *J Biol Chem* 274, 18153-18156.
- Zitzer H., Honck H.H., Bachner D., Richter D., Kreienkamp H.J., 1999b. Somatostatin receptor interacting protein defines a novel family of multidomain proteins present in human and rodent brain. *J Biol Chem* 274, 32997-33001.

