Interaction between the C terminus of a G-protein-coupled receptor and intracellular effectors may represent a crucial step in regulating signal transduction. To identify potential interacting candidates the C terminus of the somatostatin receptor subtype 1 was used as bait in a yeast two hybrid screen of a human brain cDNA library. We identified the human Skb1 sequence (Skb1Hs) as interacting protein, which is homologous to the yeast protein known Skb1 to down-regulate mitosis in Schizosaccharomyces pombe via binding to the Shk1 protein kinase; the latter is a homolog to the mammalian p21NCix/ROCX-activated protein kinases. Interaction required almost the entire C terminus of the somatostatin receptor subtype 1 including the conserved NPXY motif of transmembrane region seven; in the case of the Skb1Hs most of the N terminus and an S-adenosylmethionine binding domain were mandatory, whereas the C terminus was not essential. Interaction was verified by coexpression experiments in human embryonic kidney cells. As revealed by immunocytochemical analysis Skb1Hs expressed alone aggregates in large cytosolic clusters. When coexpressed, receptor subtype 1 and Skb1Hs were colocalized at the cell surface; these cells showed a strong increase in somatostatin binding compared with cells expressing the receptor only. This may suggest that Skb1Hs acts like a chaperone by correctly targeting the receptor to the cell surface.

Signaling through GPCRs is mediated by a limited set of intracellular transducing proteins, i.e. the heterotrimeric G-proteins, which may link ligand binding at the receptor to a wide variety of intracellular responses. Traditionally it has been assumed that all physiological effects of a given receptor can be explained by the transducing properties of either the Ga- or Gβγ-subunits that are activated by the receptor. However, recently evidence has accumulated that intracellular factors other than the G-protein subunits can affect the outcome of GPCR-mediated signaling. Thus the β2-adrenergic receptor associates in an agonist-dependent manner with the PSD-95/disc large/ZO-1 domain of the Na+/H+ exchanger regulatory factor leading to an activation of exchange activity instead of the inhibitory effect that would usually be expected from a receptor coupled to stimulatory G-proteins (1). Similarly, the interaction of metabotropic glutamate receptors with the homeric protein has been suggested to have an influence on signal transduction (2). In separate studies, it was shown that accessory proteins, receptor activity-modifying proteins (RAMPs), regulate the transport and the pharmacological properties of certain GPCRs such as the receptor for the calcitonin gene-related peptide; in the presence of RAMP1 the receptor functions as a calcitonin gene-related peptide receptor, with RAMP2 as an adrenomedullin receptor (3, 4).

The five receptors for the neuropeptide somatostatin (called SSTR1−5) couple predominantly to pertussis toxin-sensitive G-proteins of the Gαi type (5). This may lead to the inhibition of adenylyl cyclase activity or, in the appropriate cellular background, to the inhibition of voltage-gated calcium channels and the activation of inwardly rectifying potassium channels (6). However, the signaling repertoire of somatostatin is much wider and may include effects such as the activation of protein-tyrosine phosphatases (7), which are not easily reconciled with Gα-mediated signaling. For example, somatostatin appears either to enhance or to reduce the α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid/kainate receptor-mediated response to glutamate in vivo depending on whether the cells express SSTR1 or SSTR2, respectively (8).

Recently we have initiated a search for proteins that may interact with SSTRs and might thus modify signal transduction properties of somatostatin receptor subtypes such as SSTR1 or SSTR2. As a first result, we have shown that the C terminus of the rat SSTR2 associates with the PSD-95/disc large/ZO-1 domain of the cortactin-binding protein 1 and that binding of somatostatin to SSTR2 stimulates the interaction between the receptor and cortactin-binding protein 1 (9). In addition we have shown that SSTR2 associates also with another multidomain protein, SSTRIP, which besides a PSD-95/disc large/ZO-1 domain contains several ankyrin repeats, an Src homology 3 domain, several proline rich regions, and a sterile alpha motif (10).

In extending our studies we report here the results of a yeast two hybrid screen using the intracellular C terminus of the SSTR1 as the bait. As the C-terminal sequences of the SSTR are largely divergent, we expected that proteins interacting with this region may determine the specificity between the receptor subtypes and effectors such as ion channels, protein kinases, or phosphatases. Here we show that the C terminus of the SSTR1 specifically interacts with the human Skb1Hs protein, which is homologous to the yeast protein Skb1 known to down-regulate mitosis in Schizosaccharomyces pombe via binding to the Shk1 protein kinase; the latter is a homolog to the...
mammalian p21<sup>dc342/Rac</sup>-activated kinases involved e.g. in cell viability, normal morphology, and mitosis (11, 12). Delineation of the sequence motifs essential for the Skb1Hs and SSTR1 interaction are provided along morphological and biochemical evidence that the two proteins interact with each other. When cotransfected in human embryonic kidney (HEK) cells SSTR1 and Skb1Hs are colocalized at the cell surface; these cells also exhibited a greatly increased somatostatin binding compared with cells transfected with SSTR1 only, suggesting that Skb1Hs may function like a chaperone or RAMP protein.

**MATERIALS AND METHODS**

**Yeast Two Hybrid Screen**—A cDNA fragment (nucleotide residues 946–1173) coding for the last 77 amino acids of the C terminus of the rat SSTR1 (13) was cloned into the Gal4-binding domain containing yeast bait vector pAS-2 (CLONTECH Laboratories, Inc., Palo Alto, CA). After transformation into the yeast reporter strain Saccharomyces cerevisiae CG1945 (CLONTECH) a human brain cDNA library in the Gal4 activation domain fish vector pACTII (CLONTECH) was screened for interacting proteins using protocols available from CLONTECH and from the Gietz laboratory. Of a total of 1.1 × 10<sup>6</sup> transformants seven true positive clones were identified by the β-galactosidase filter lift assay (14). The specific interaction of the positive clones with the C terminus of SSTR1 was verified by a negative control using a cDNA fragment coding for the C terminus of the rat SSTR2. DNA isolated from the positive clones was sequenced by the dideoxy chain termination method.

**Expression in HEK Cells and Coimmunoprecipitation**—An expression vector containing an N-terminal T7-epitope tag in frame with the human hSSTR1-coding sequence (referred to as NT7-tagged SSTR1) was obtained by cloning the hSSTR1 cDNA into a modified pcDNA3 plasmid (Invitrogen, Leek, The Netherlands) as described (16, 17). Full-length human Skb1Hs was constructed from the initial clone (encoding amino acids 55–637) obtained from the yeast two hybrid library, and an expressed sequence tag clone containing the N terminus (amino acids 1–64). The cDNA was cloned into modified pcDNA3 vectors coding for either N-terminal or C-terminal e-Myc tags (Invitrogen). The cDNAs for NT7 tag SSTR1 and the Skb1Hs were then coexpressed in HEK cells by transient transfection using the calcium phosphate method (18). For immunoprecipitations, cells were lysed in radioimmunoprecipitation buffer (1% Nonidet P-40, 0.5% sodium deoxycholate, 0.1% SDS, 150 mM NaCl, 50 mM Tris-HCl, pH 8.0, 10 mM sodium pyrophosphate, 0.2 mM phenylmethylsulfonyl fluoride, 10 mM NaF, 1 μg/ml pepstatin, 5 mM EDTA) on ice for 10 min and centrifuged at 15,000 × g for 20 min at 4 °C. The epitope-tagged receptor was precipitated from the supernatant fraction using the monoclonal T7 antibody (Novagen, Madison, WI) and protein A-Sepharose (Amersham Pharmacia Biotech) as described (17). Precipitates were analyzed by Western blotting using either T7 or c-Myc (Sigma) monoclonal antibodies as primary and a goat anti-mouse IgG-conjugated to alkaline phosphatase (Santa Cruz Biotechnology Inc., Santa Cruz, CA) as a secondary antibody.

**Site-directed Mutagenesis**—Deletion mutants of SSTR1 in the expression vector NT7 tag pcDNA3 were obtained by polymerase chain reaction using mutagenic primers introducing a stop codon and the appropriate restriction sites (16). Deletion mutants in the yeast two hybrid vectors pAS-2 (for SSTR1 mutants) and pACTII (for Skb1Hs mutants) were obtained similarly by polymerase chain reaction.

**Confocal Microscopy**—For the colocalization of human SSTR1 and c-Myc-tagged Skb1Hs tags (at the C terminus), transfected HEK cells were plated onto poly-D-lysine-coated glass coverslips. After incubation in normal growth media for 2 days, cells were fixed and permeabilized as described (16). After incubation with a mixture of T7 mouse monoclonal antibody (1:10,000) and Skb1Hs specific rabbit polyclonal antiserum (1:2000) in phosphate-buffered saline containing 2% normal fetal calf serum overnight at 4 °C, Cy2-conjugated goat anti-mouse and Cy3-conjugated goat anti-rabbit were used as secondary antibodies (9). Cells were viewed with a confocal microscope (Leitz laser scanning microscope) using specific settings for Cy2 (argon laser/excitation at 488 nm/emission band pass 510–525 nm) and Cy3 (helium-neon laser/exci-
Identification of an SSTR1-interacting Protein—To identify potential SSTR1-interacting proteins the C terminus of SSTR1 (starting with the amino acid sequence SCANPILY in the C-terminal part of transmembrane region 7 and thus including the canonical NPXXY motif) was used as a bait in a yeast two hybrid screen. Seven positive clones were obtained from a human brain cDNA library four of which showed only a weak response in the β-galactosidase assay; sequencing revealed that they were either identical with syntrophin β2 (19) or similar to a protein interacting with the viral oncoprotein Tax (20) or exhibited sequences not listed in the GenBank data base (two clones). The remaining three clones with identical inserts were identified as the human Skb1Hs protein (12, 21), which is structurally and functionally homologous to the yeast protein Skb1; the latter has been shown to negatively regulate the mitosis in the fission yeast S. pombe (11, 12). The Skb1Hs clone contained almost the full-length coding sequence of 637 amino acids lacking only 55 residues at its N terminus. The interaction of SSTR1 with Skb1Hs was by far the strongest; in β-galactosidase filter assays a significant response could usually be obtained within a few minutes, whereas for the other clones a reaction time of more than an hour was necessary to obtain a signal of similar intensity (data not shown).

Delineation of the Interacting Regions of Skb1Hs and SSTR1—The structure of the Skb1Hs protein exhibits only one obvious motif, the S-adenosylmethionine binding domain, which does not allow any conclusions regarding its interaction with the C terminus of SSTR1 (Fig. 1A). In an attempt to delineate the regions involved in the interaction of the two partners, several deletion mutants were generated from the initial target vector Skb1Hs obtained from the human brain cDNA library; they were cotransformed with the SSTR1 fragment in yeast cells which grow on His-deficient plates only when cells contained both interacting partners. Growth of cotransformed yeast cells containing various 3-AT concentrations, and the strength of the interactions between the interacting partners were verified by β-galactosidase assays confirming that most of the Skb1Hs protein is involved in the interaction with the C terminus of SSTR1.

To delineate the C-terminal receptor interacting region, yeast cells cotransformed with Skb1Hs and various SSTR1 constructs were analyzed by transformation of yeast cells with pACTII-Skb1Hs and pAS2-SSTR1 deletion mutants as indicated. Numbers of the first and last amino acids of the constructs are shown. As a negative control the corresponding region of SSTR2 in the pAS2-vector was used. TM, transmembrane region; B, growth inhibition assay in liquid culture. Shown are the growth inhibition curves of SSTR1 deletion constructs with progressive truncation at the N terminus. The dose-response data were subjected to nonlinear regression analysis using the GraphPad Prism software (GraphPad Inc., San Diego, CA). Yeast transformants expressing both plasmids were cultured in His-deficient liquid medium containing various concentrations of 3-AT. The optical density of the culture at 600 nm after 3 days is given as the fraction of growth obtained in the absence of 3-AT. Values are the mean ± S.D. of triplicate determinations. C, list of IC50 values calculated from B. No exact IC50 values could be calculated for the SSTR2, 305–369 and SSTR1, 328–391 constructs because of the low affinity of the interaction.

![Fig. 2. Delineation of the region in the SSTR1 C terminus required for interaction with Skb1Hs.](image)
SSTR1_316–391 construct showed strong growth response with an IC_{50} of 33.5 mM 3-AT (Fig. 2, B and C), whereas deletions at the N terminus (SSTR1_{322–391} and SSTR1_{328–391}) resulted in an increase in the sensitivity to 3-AT with an IC_{50} of 5.6 and below 2 mM 3-AT, respectively. The twelve amino acid residues of the N terminus of the initial SSTR1_{316–391} construct are apparently essential for the full interaction with the Skb1Hs protein. This region includes the highly conserved NPILY motif in the seventh transmembrane region also present in SSTR2, the rat m-opioid receptor, and SSTR4 also appear as several differentially glycosylated proteins migrating as distinct bands (B).

### TABLE I

| Amino acid sequence comparison of the C terminus of SSTR1 and -4 |
|---------------------------------------------------------------|
| Numbering refers to the human hSSTR1 sequence and is compared to rat rSSTR1_{310–391} and rSSTR4_{346–362}. Amino acids identical in all three sequences are indicated by white letters on a gray background. |

|     | SSTR1 | rSSTR1 | rSSTR4 |
|-----|-------|--------|--------|
| 316 | hSSTR1 | rSSTR1 | rSSTR4 |
|     | hSSTR1 | rSSTR1 | rSSTR4 |
| 340 | hSSTR1 | rSSTR1 | rSSTR4 |
| 341 | hSSTR1 | rSSTR1 | rSSTR4 |
| 370 | hSSTR1 | rSSTR1 | rSSTR4 |
| 391 | hSSTR1 | rSSTR1 | rSSTR4 |

Fig. 3. Coimmunoprecipitation of human SSTR1 and Skb1Hs. A, HEK cells were transfected either with Skb1Hs cDNA alone or in combination with NT7-tagged SSTR1 cDNA. After lysis in radioimmune precipitation buffer containing either 0.1% or 1% SDS, the receptor was precipitated using the T7 antibody; precipitates were then analyzed by Western blotting using either the c-Myc antibody (left panel) or the T7 antibody (right panel). B, HEK cells were transfected with Skb1Hs cDNA alone or in combination with cDNAs encoding either NT7-tagged SSTR1, -2, -4, or the rat m-opioid receptor. After lysis and immunoprecipitation as described in A, Western blotting was performed with c-Myc (upper panel) and T7 (lower panel) antibodies. IP: immunoprecipitation; IB: immunoblotting; marker, full range rainbow protein molecular weight marker (Amersham Pharmacia Biotech); open arrows indicate the position of the precipitated Skb1Hs protein at 72 kDa; SSTR1 appears in multiple bands; the lowest band (68 kDa) presumably corresponds to a monomeric receptor (calculated molecular mass, 43 kDa), which is glycosylated. In addition, filled arrowheads indicate positions of 165-, 155-, and 105-kDa proteins representing most likely differentially glycosylated receptors (or multimers) (A). SSTR2, the rat μ-opioid receptor, and SSTR4 also appear as several differentially glycosylated proteins migrating as distinct bands (B).

To investigate the interaction between human SSTR1 and Skb1Hs in a mammalian system the full-length constructs were cotransfected in HEK cells. For identification the proteins carried either a T7 tag at the N terminus of SSTR1 or a c-Myc tag at the C terminus of Skb1Hs. When the receptor was immunoprecipitated from lysates of cotransfected HEK cells using a T7 monoclonal antibody, analysis of the resulting immunoprecipitate by Western blotting revealed the presence of c-Myc-tagged Skb1Hs as identified by a band at 72 kDa. This band was absent when the SSTR1 was omitted from the transfection mixture (Fig. 3A). Similar results were obtained with a Skb1Hs construct carrying the c-Myc epitope tag at the N terminus (data not shown). As already inferred from the strong β-galactosidase reaction in the yeast two hybrid experiment, the interaction between SSTR1 and Skb1Hs appeared to be very strong because it could still be observed when lysis of the cells was carried out in the presence of 1% SDS.

As indicated already by experiments in the yeast system, no interaction between SSTR2 and Skb1Hs was observed in coimmunoprecipitation experiments (Fig. 3B). Similarly, coexpression of a NT7 epitope-tagged μ-opioid receptor did not lead to an interaction between this receptor and the Skb1Hs protein. However, NT7-tagged SSTR4, which is most similar to the C terminus of SSTR1 in its primary structure (Table I), was able to interact with c-Myc-tagged Skb1Hs in HEK cells (Fig. 3B).

To verify the specificity of the interaction between the C-terminal regions of the SSTR1 and Skb1Hs, several deletion mutants of the NT7-tagged SSTR1 C terminus were constructed and used for coexpression in HEK cells. In coimmunoprecipitation assays the construct NT7-tagged SSTR1_{1–370} (lacking the last 21 amino acid residues efficiently precipitated the c-Myc-tagged Skb1Hs protein, whereas further truncations at the C terminus (NT7-tagged SSTR1_{1–346} or NT7-tagged SSTR1_{1–327}) abrogated the interaction with Skb1Hs indicated by the absence of the latter in the immunoprecipitate (Fig. 4A). These results are consistent with those obtained in the yeast two hybrid system (Fig. 2). Similar results were obtained when c-Myc-tagged Skb1Hs was precipitated, and T7-tagged SSTR1 deletion mutants were detected by Western blotting using the T7 antibody. Only full-length NT7-tagged SSTR1_{1–391} and NT7-tagged SSTR1_{1–370} were observed in the precipitates, whereas shorter deletion constructs were not detected.

Interaction of the Human SSTR1 with the Skb1Hs Protein in HEK Cells—To investigate the interaction between human
Confocal microscopic analysis of HEK cells transfected with c-Myc-tagged Skb1Hs alone revealed that the protein was found exclusively in intracellular clusters, which do not resemble any known cellular structures (Fig. 5). Such intracellular clusters or aggregates have been observed in several diffuse bands ranging from molecular mass of 65–160 kDa; truncated receptor proteins of 55 (*) and of 52 kDa (**) are observed. Precipitation was performed using the c-Myc antibody, and immunoblots were probed with c-Myc (upper panel) and T7 (lower panel) antibodies. IP, immunoprecipitation; IB, immunoblotting.

To investigate the function of the interaction of Skb1Hs with the C terminus of SSTR1, we examined the number of binding sites for radioactively labeled somatostatin when SSTR1 was expressed in HEK cells in the absence or presence of Skb1Hs. Binding assays demonstrated a dramatic increase of specifically bound radioligand to those cells cotransfected with SSTR1 and Skb1Hs compared with cells transfected with SSTR1 only (Table II). These results suggest that the interaction between Skb1Hs and SSTR1 is an important step for transporting the receptor to the cell surface.

DISCUSSION

The data presented here clearly identify a specific interaction between the C terminus of SSTR1 and the human homolog of a kinase-binding protein from the fission yeast S. pombe. When trying to identify the regions of both proteins involved in...
this interaction, we determined that large portions of the bait as well as of the fish were necessary to obtain a strong response in the yeast two hybrid system. This suggests that the interaction is not mediated by a single domain but that the intact tertiary structure of the whole Skb1Hs protein may be required to bind the SSTR1 C terminus.

In SSTR1, only the extreme C terminus could be deleted without abolishing the interaction between both proteins. Regions necessary for the interaction are located close to or even within the seventh transmembrane region including the NPXXY motif common to many GPCRs. It is interesting to note that SSTR4 was the only other receptor tested that could be coimmunoprecipitated with the Skb1Hs protein. In respect to its C terminus, SSTR4 is the subtype with closest homology to its C terminus, SSTR1; the homology extends up to the amino acid position 360 in the SSTR1 sequence (Table I), a region essential for the interaction of SSTR1 with Skb1Hs both in yeast and in HEK cells.

The function of the Skb1 protein is unclear at present in the yeast as well as in human cells. In S. pombe, it was suggested that Skb1, through its interaction with the Shk1 kinase, might influence mitogen-activated protein kinase pathways and the organization of the cytoskeleton, leading to changes in cell morphology (11). When we analyzed activation of the mitogen-activated protein kinase by somatostatin in HEK cells expressing SSTR1, we observed efficient activation of this pathway regardless if Skb1Hs was coexpressed or not (data not shown). However, HEK cells express endogenous Skb1Hs (21), which might be sufficient to fulfill a role in SSTR1 signal transduction. Skb1Hs, as shown here in cells overexpressing this gene, is localized in undefined cytosolic structures. This localization may be a consequence of the lack of appropriate interaction partners within the transformed cells, as has been observed before for proteins involved in the targeting of other neurotransmitter receptors (22). Accordingly, a dramatic relocalization of Skb1Hs was observed in cells coexpressing SSTR1, leading to the detection of Skb1Hs-specific fluorescence at the plasma membrane where it colocalizes with SSTR1.

The function of the novel interaction reported here remains unclear at present; with respect to signal transduction by SSTR1, Skb1Hs has not been able to confer the ability to couple to a G-protein gated inwardly rectifying potassium channel when coexpressed in Xenopus oocytes. However, our findings may present an explanation of several inconsistencies in the literature. Thus functional coupling of SSTR1 to the adenylyl cyclase system has been observed in some but not all experiments (23–25). In addition, inhibition of voltage-gated calcium channels by SSTR1 has been disputed (26, 27). These discrepancies may be attributed to the cellular environment, in particular to the presence of the Skb1Hs protein. Our data show that coexpression of Skb1Hs augments functional expression of the SSTR1 protein at the cell surface. Presumably Skb1Hs may be required for efficient targeting of the receptor to the cell surface; low expression levels of Skb1Hs may interfere with the functional insertion of SSTR1 into the plasma membrane supporting the idea that Skb1Hs functions as a chaperone- or RAMP-like protein. Interestingly, Skb1Hs has been found to be tightly associated with the protein pICln (21); expression of pICln in Xenopus oocytes regulates the appearance of a swelling-induced chloride channel in the oocyte membrane (28, 29). Thus pICln and Skb1Hs may play a more general role in the expression of membrane proteins.

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Interaction of the Somatostatin Receptor Subtype 1 with the Human Homolog of the Shk1 Kinase-binding Protein from Yeast
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