Somatostatin Receptors

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Overview

Somatostatin (somatotropin release-inhibiting factor, SRIF) is a cyclic peptide widely expressed throughout the CNS, endocrine tissues and gastrointestinal tract. The 14 amino acid peptide, somatostatin (SRIF-14), was first identified and isolated from ovine hypothalamic extracts as a potent inhibitor of growth hormone release from the pituitary. Subsequently, a longer N-terminally extended form (SRIF-28) was identified. SRIF exerts a wide range of biological actions, including inhibition of secretion of growth hormone, insulin, glucagon and gastrin as well as other hormones secreted by the pituitary and gastrointestinal tract. Somatostatin also acts as a neuromodulator in the CNS and shows anti-proliferative effect on a wide range of cancer cells. A rat neuropeptide, named cortistatin (CST), with strong homology to SRIF has also been cloned. Depending on the species, CST is a tetradecapeptide, sharing up to 11 amino acids with SRIF. The human homolog of CST appears to be a heptadecapeptide (CST-17). By analogy with SRIF, there may also be a larger isoform of CST, i.e. CST-29. Although various physiological parameters, including transitions between sleep phases, consolidation of short- and long-term memory and locomotor activity, respond in an apparently transmitter-specific manner to SRIF and CST, the latter is an endogenous ligand at SRIF receptors, with nanomolar affinity for each subtype. The existence of specific CST receptors has not been demonstrated so far, although it was suggested that MGRX2 may play such a role.

SRIF and CST act via a family of G protein-coupled receptors, of which five subtypes (sst_1-sst_5) have been cloned and characterized from various species. Sequence homology is 39-57% among the five subtypes, each being highly conserved across species. Based on structural and operational features, they can be divided into two groups: SRIF-1 includes sst_2, sst_3 and sst_5 receptors while SRIF-2 consists of sst_1 and sst_4 receptors, distinguished by high affinity of cyclic peptides such as octreotide (SMS-201-995), seglitide (MK-678) and lanreotide (BIM-23014) for the SRIF-1 group.

Molecular biological techniques and subtype selective antibodies have been used to determine the distribution of the sst_1-sst_5 gene transcripts and receptor protein in brain and periphery. Selective peptidic agonists at sst_1 (CH-275) and sst_4 receptors (NNC 26-9100) have been described, as has an sst_3 receptor antagonist (sst3-ODN-8). However, the use of peptides for *in vivo* experiments is limited by pharmacokinetic constraints that may be addressed by the recent description of non-peptide agonists selective for each of the five somatostatin receptors. Further, non-peptide antagonists such as SRA880 (sst1 selective), ACQ090 (sst3 selective) and sst4 selective β peptide agonists which all show adequate stability and bioavailability have been described more recently.

Studies utilizing subtype selective SRIF analogs in both *in vivo* and *in vitro* experiments demonstrate that sst_2 receptors are the major player in the SRIF receptor family with broad inhibitory effects on the endocrine secretion, e.g. growth hormone, insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide and secretin, as well as the exocrine secretion, e.g. gastric acid, intestinal fluid and pancreatic enzymes. Sst_2 receptors also seem to play a major role in various forms of gastroenteropancreatic cancers, in epilepsy and pain. The sst_1 receptor may function as an autoreceptor at least in basal ganglia and the eye. Sst_3 receptors are enigmatically localized to neuronal cilia, and sst_3 antagonists have marked behavioral effects. Sst_4 receptors are highly expressed in the lung, but their role remains to be defined, although in the mouse they modulate epileptic activity. Sst_5 receptors mediate inhibition of insulin release from the pancreatic β-cells in addition to regulating growth hormone release. Currently, octreotide and lanreotide are in clinical use for the treatment of acromegaly, diarrhea and various gastro-enteropancreatic tumors, whereas In-111 pentreotide is used for whole body tumor imaging.

Somatostatin Receptors

Currently Accepted Name [a]	sst_1	sst_2	sst_3	sst_4	sst_5
Alternate Names	SRIF-2	SRIF-1	SRIF-1	SRIF-2	SRIF-1
Structural Information	391 aa (human)	369 aa (human)	418 aa (human)	388 aa (human)	364 aa (human)
Selective Agonists	CH-275, L-797,591	MK-678 (Seglitide, **(S1316)**), BIM-23027 **(B0434)**, L-054,522, L-779,976	L-796,778	NNC 26-9100, L-803,087	L-817,818
Selective Antagonists	NVP-SRA880	Cyanamid-154806 **(C2490)**	sst3-ODN-8, NVP-ACQ090	Not known	BIM-23056 **(B4310)**
Signal Transduction Mechanisms	G_i (cAMP modulation)	G_i (cAMP modulation), PLC/PKC/MAPKinase	G_i (cAMP modulation) PLC/PKC/MAPKinase	G_i (cAMP modulation)	G_i (cAMP modulation), PLC, PKC, calcium
Radioligands of Choice	[^{125}I]-[Tyr^{25}]-SRIF28	[^{125}I]-[Tyr^{25}]-SRIF28	[^{125}I]-[Tyr^{25}]-SRIF28	[^{125}I]-[Tyr^{25}]-SRIF28	[^{125}I]-[Tyr^{25}]-SRIF28
Tissue Expression	Brain, cortex, eye, hypothalamus	Brain, pancreas, pituitary, GI tract	Neuronal cilia, lymphocytes	Brain, hippocampus, lung	Brain (?), pituitary, vascular smooth muscle
Physiological Function	Autoreceptor	Inhibition of hormone release, inhibition of tumor growth	Apoptosis, tumor cell growth inhibition	Tumors ?	Inhibition of insulin release, tumor growth?
Disease Relevance	Not known	Acromegaly, GEP tumors, pain, GI tract disorders, epilepsy	Sarcomas	Not known	Acromegaly

Abbreviations
BIM-23027: c[N-methyl-Ala-Tyr-D-Trp-Lys-Abu-Phe]
BIM-23056: D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH_2
CH-275: des-AA1,2,5(D-Trp8,Iamp9)-SRIF
Cyanamid-154806: AC-4-NO2-Phe-c[D-Cys-Tyr-D-Trp-Lys-Thr-Cys]-D-Tyr-NH_2
GEP: Gastro-enteropancreatic
GI: Gastrointestinal
MK-678 (Seglitide): c[N-Methyl-Ala-Tyr-D-Trp-Lys-Val-Phe]
L-797,591: (2R)-N-(6-Amino-2,2,4-trimethylhexyl)-3-(1-naphthyl)-2-({[(2-phenylethyl)(2-pyridin-2-ylethyl)amino]carbonyl}amino)propanamide
L-054,522: tert-Butyl (bS)-b-methyl-N-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl}-D-tryptophyl-L-lysinate
L-779,976: (bS)-N-{[3-(Aminomethyl)cyclohexyl]methyl}-b-methyl-N-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl}-D-tryptophamide
L-796,778: Methyl (2S)-6-amino-2-[((2R)-2-[[({(1S)-1-benzyl-2-[(4-nitrophenyl)amino]-2-oxoethyl}amino)carbonyl]amino}hexanoyl)amino]hexanoate
L-803,087: Methyl (2S)-5-{[amino(imino)methyl]amino}-2-{[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino}pentanoate or methyl N2-[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]-L-argininate
L-817,818: (2R)-2-Aminopropyl N2-{[2-(2-naphthyl)-1H-benzo[g]indol-3-yl]acetyl}-L-lysinate
NNC 26-9100: I-[3-[N-(5-Bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)aminopropyl]-3-[3-(1H-imidazol-1-yl)propyl]-thiourea
NVP-ACQ090: [4-(3,4-Difluoro-phenyl)-piperazin-1-yl]-{(4S,4aS,8aR)-2-[(S)-3-(6-methoxy-pyridin-3-yl)-2-methyl-propyl]-decahydro-isoquinolin-4-yl}-methanone
NVP-SRA880: [3R,4aR,10aR]-1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-1-methyl-benz[g] quinoline-3-carboxylic-acid-4-(4-nitro-phenyl)-piperazine-amide, hydrogen malonate
sst3-ODN-8: Carbamoyl-des-AA1,2,4,5,12,13[D-Cys^3,D-Arg^8(Me,2-naphthoyl)]-SRIF
[^{125}I]-[Tyr^{25}]-SRIF$_{28}$: 3-[^{125}I]iodotyrosyl^{25}-SRIF-(Leu^8,D-Trp^{22},Tyr^{25})

Footnotes