Endocrine, *vol. 20, no. 3, 255–264, April 2003* 0969–711X/03/20:255–264/$20.00

Somatostatin and Somatostatin Receptor Physiology

Philip Barnett

Pituitary Center, Cedars Sinai Medical Center, Los Angeles, CA

Since the discovery of somatostatin (SST) over three decades ago, its ubiquitous distribution and manifold functions are still being documented. SST is synthesized in the hypothalamus and transported to the anterior pituitary gland where it tonicaly inhibits GH and TSH secretion as well as being responsible for GH pulsatile release. Several internal feedback loops, sleep, exercise, and chemical agents control and influence SST release. SST also impacts the function of a wide variety of cells and organ systems throughout the body. Knowledge of the structures of the SSTs has resulted in recognition of the essential four core conserved residues responsible for their actions. The SSTs act through six separate SST cell surface receptors (SSTRs), members of the family of G protein-coupled receptors. Receptor ligand binding (SST/SSTR) results in cellular activities specific for each receptor, or receptor combinations, and their tissue/cell localization. Understanding the structure/function relationship of the SSTs and their receptors, including the internalization of SST/SSTR complexes, has facilitated the development of a variety of novel pharmacologic agents for the diagnosis and treatment of neuroendocrine tumors and unfolding new applications.

Key Words: Somatostatin; somatostatin receptor; growth hormone; thyroid-stimulating hormone.

Introduction

Originally identified by Krulich et al. *(1)*, in 1968, and isolated and characterized by Brazeau et al. *(2)*, in 1973, human somatostatin (SST) (somatotropin release-inhibiting hormone, somatotropin release-inhibiting factor) was located in the hypothalamus by Pelletier et al. *(3)* in 1977. SST has subsequently been detected in almost every tissue and organ system, nerve terminal, and specialized glandular cell, in several molecular sizes and acting through six separate receptor (SSTR) subtypes. In addition to modulating the function of higher brain centers, this hypophysiotropic hormone exerts an inhibitory influence on different target organ hormone and exocrine secretory activities *(4)* and cell proliferation *(5)*, while separately promoting apoptosis. SST is extremely versatile, functioning as a neurohormone, neurotransmitter, and autocrine/paracrine hormone.

Received January 7, 2003; Accepted January 9, 2003.

Author to whom all correspondence and reprint requests should be addressed: Philip Barnett, Pituitary Center, Cedars Sinai Medical Center, 8635 West 3rd Street, Suite 490W, Los Angeles, CA 90048. E-mail: barnettp@CSHS.org

Somatostatin

SST is a cyclic tetradecapeptide synthesized in the hypothalamus and responsible for inhibitory influences on the secretion of growth hormone (GH) and thyroid-stimulating hormone (TSH) from the anterior pituitary gland *(6,7)*. In addition to these major functions and site of initial localization, SST and SSTRs are ubiquitous in the human body, where they exert multiple physiologic effects (Table 1).

SST is synthesized as two bioactive proteins: the predominant, but functionally less active SST molecule consisting of 14 amino acids (SST-14) with a disulfide bond linking the cysteine residues at positions 3 and 14, and a larger more potent molecular form, SST-28 *(8)*, which is a congener of SST-14 extended at the amino terminal *(6,9)*. Both are secreted from the hypothalamus in physiologic concentrations, and unless otherwise indicated, the term SST refers to both SST-14 and SST-28. A 25 amino acid product, as well as several larger molecular forms of SST, have been described, ranging from 11.5 to 15.7 kDa *(6)*. The 116 amino acid SST preprohormone, synthesized in the anterior hypothalamic periventricular nuclei, consists of a 24 amino acid signal peptide connected to the 92 amino acid prohormone, which comprises a 64 amino acid peptide connected to SST-28 *(10)*. SST-28 and the enzymatically cleaved SST-14 are transported from there by axoplasmic transport to the median eminence *(11)* and nerve terminals in the vicinity of the hypophyseal portal vessels, from where they travel to the anterior pituitary gland in the portal system *(12,13)*. The SSTs have a very short circulation half-life of 1.5–3 min *(6,14)*. The implication of this is that SST-producing cells, or nerve ending stores of SST, are probably generally close to the target cells that they influence.

SST-28 is the major SST molecule detected in the fetal hypothalamus at 10 wk of gestation. With fetal maturation, there is an increase in the amount of SST-14 with a parallel increase in the number of SST-containing neurons located in the anterior portion of the arcuate nucleus *(15,16)*. Growth hormone–releasing hormone (GHRH), the counterbalance of SST in the regulation of GH secretion, is first detected

Table 1
Physiologic Actions of Somatostatin[a]

- Inhibition of GH and TSH secretions from anterior pituitary
- Inhibition of cell proliferation
- Inhibition of pancreatic secretions
  - Endocrine—insulin, glucagon, pancreatic polypeptide
  - Exocrine—bicarbonate and digestive enzymes
- Inhibition of GI peptide secretions—gastrin, secretin, cholecystokinin, VIP, gastric inhibitory polypeptide, motilin, enteroglucagon, neurotensin, gastric acid, peptide intrinsic factor, bile, and colonic fluids
- Inhibition and modulation of GI functions
  - Bowel motility, gastric emptying, GI transit time, and small bowel segmentation
  - Gallbladder contractility and bile flow
  - Splanchnic and liver blood flow
  - Intestinal absorption of glucose, fructose, galactose, lactose, amino acids, calcium, glycerol, xylose, and triglycerides
  - Mucosal cell proliferation
- Stimulation of GI water and electrolyte absorption
- Inhibition of thyroxine, triiodothyronine, and calcitonin thyroid secretion
- Inhibition of renal and adrenal secretion of renin and aldosterone
- Inhibition of vascular smooth muscle contractility
- Inhibition of activated immune cells
- Inhibition of CNS functions
  - Behavior
  - Cognition
- Inhibition of peripheral nervous system functions
  - Motor
  - Sensory
- Promotion of apoptosis

[a]Adapted from refs. *5–8, 119, 124, 138, 201, 215,* and *216.*

in the hypothalamus at 18 wk of gestation *(17)*. The distribution of SST-containing neurons is species specific *(3,18–20)*. In humans, SST-containing dense core cytoplasmic vesicles (80–110 nm in diameter), found in cell bodies and nerve endings *(5)*, are located in several nuclei of the hypothalamus (particularly the preoptic, suprachiasmatic, and retrochiasmatic nuclei of the anterior paraventricular region *[19]*), the external zone of the median eminence, and the neurovascular zone of the pituitary stalk *(19)*. Other nonhypothalamic brain distribution sites of SST include the cortex, brain stem, pineal gland, retina, optic nerve, auditory nerve, and spinal cord *(21)*. Precursors of SST have been detected in the anterior pituitary, suggesting that SST may in fact be synthesized there as well, where it acts through autocrine and paracrine mechanisms *(22)*. Outside the central nervous system (CNS), SST has been demonstrated in several different sites including the endocrine (α-, β-, δ-cells) *(21, 23)* and exocrine pancreas, gastrointestinal (GI) tract (including upper GI D-cells *(24–26)*, salivary glands, thyroid epithelial and C-cells, kidneys, prostate, placenta, lymphoid cells and tissues, immune system, blood vessel walls, as well as in the circulation *(6,7)*.

Human anterior pituitary GH secretion is sporadic and unique for each individual, with an ultradian rhythm *(27)*. GH secretory "bursts" are irregular, 10–20/d, occurring predominantly at night with the onset of rapid eye movement (REM) sleep, when they are of greatest amplitude. Of note is the fact that SST increases REM sleep *(28)*. In adults, there is a basal rate of GH secretion throughout the day, at concentrations so low that for the most part GH is "undetectable," other than by ultrasensitive assays. As a neurohormone, the major role of hypothalamic SST is tonic inhibition of the basal and GHRH-stimulated secretion of GH from anterior pituitary somatotrophs *(29)*. Studies in rats using SST and GHRH antibodies *(27)* have demonstrated that SST is responsible for GH pulsatility as well as trough levels, while GHRH plays a role in spontaneous GH bursts *(27,30, 31)*. GH pulsatility is generated by the 180° out-of-phase secretion of GHRH and SST every 3 to 4 h *(27)*. Rebound GH hypersecretion, in normal individuals, has been demonstrated following SST infusion withdrawal (SSIW), most likely owing to sensitization of somatotrophs to GHRH *(32–36)*, and is enhanced even further in the presence of GHRH *(32,37–39)*. This process is responsible for controlling GH pulsatile secretion. Thus, SST withdrawal determines the timing and duration of GH secretory bursts while GHRH determines the magnitude. SST infusion suppresses insulin and glucagon, and glucose transiently, in addition to GH, with rebound hypersecretion of insulin and glucagon post-SSIW. In obese individuals, GH secretion is inversely related to body mass index *(40,41)*. It has been postulated that this may be owing to increased hypothalamic SST secretion *(42)* and/or elevated plasma free fatty acid levels *(43–45)*. Recently, it has been demonstrated that obesity is also associated with a blunted peak GH following SSIW plus GHRH, in addition to an absent increase in GHRH-induced GH secretion *(46)*. The persistence of GH hyposecretion in this setting of diminished SST secretion suggests that there are several factors responsible for the state of low GH secretion, or relative GH deficiency, in obesity.

SST inhibits GH secretion but exerts no influence on somatotroph GH synthesis, while hypothalamic GHRH promotes GH synthesis, through stimulation of GH mRNA transcription, and secretion *(47,48)*, mainly of stored vs newly synthesized hormone *(49)*. Hypothalamic SST secretion is promoted by dopamine, substance P, neurotensin, glucagon, hypoglycemia, several amino acids, acetylcholine, α_2-adrenergic agonists, vasoactive intestinal polypeptide (VIP), and cholecystokinin, and it is inhibited by glucose *(6,50,51)*. Several feedback loops facilitate GH autoregulation. GH itself stimulates hypothalamic SST release *(52)* and is probably responsible for the reduced somatotroph GH response to GHRH following GH exposure *(53,54)*. Chronic GHRH exposure results in reduced GH secretion by GHRH *(55,56)*, possibly owing to depletion of somatotroph stores of GH, or a

decrease in GHRH-binding sites *(57)*. GHRH and SST both autoregulate their own secretions *(58)*, while GHRH additionally stimulates SST secretion *(59)*.

SST inhibits the GH secretion induced by sleep, exercise, insulin hypoglycemia, arginine, morphine, and L-dopa. Insulin-like growth factor-1 (IGF-1), synthesized mainly in the liver, by GH action, feeds back on both the hypothalamus (stimulating SST release *[60]*) and the pituitary (inhibiting GH gene transcription *[61,62]* and GH secretion) *(63)*. The mechanisms by which SST reduces the plasma IGF-1 concentration are through both a decrease in somatotroph GH secretion and a decline in hepatocyte GH sensitivity *(64)*. The well-recognized decline in GH secretion with advancing age is owing to a marked decrease in hypothalamic GHRH secretion together with an increase in SST secretion *(65)*. Hypothalamic GHRH release may be inhibited directly by SST neurons that impinge on GHRH-containing perikarya in the hypothalamic arcuate nucleus *(66)*. Many other hormones, neurotransmitters, and secretagogues help fine-tune the control of GH secretion, some independently of the GHRH/SST control pathways, such as ghrelin/leptin *(67–69)*. Chronic cell stimulation by SST results in SSTR desensitization owing to both receptor internalization through endocytosis and phosphorylation. Rates of phosphorylation, desensitization, and internalization vary between SSTR subtypes *(70)*.

The mechanism by which α-adrenergic blockade suppresses GH secretion is through inhibition of GHRH release together with stimulation of SST secretion *(71)*. GHRH-induced GH release is increased by β-adrenergic blockade, owing either to decreased hypothalamic SST secretion or to a direct β-adrenergic effect on the pituitary gland *(72)*. Increased GH secretion following administration of epinephrine results from a decline in SST secretion *(73)*.

SST and GHRH are responsible for controlling the number of somatotrophs involved in GH secretion—SST decreasing, and GHRH increasing their numbers. GHRH also increases the amount of GH secreted per cell *(74)*. GH secretagogues (GHSs) increase the number of somatotrophs secreting GH but do not alter the quanta of GH released per cell *(74)*. GHSs and SST may hyperpolarize and depolarize the same somatotroph cells. Current data confirm that GHSs induce GH secretion independent of GHRH and SST *(75–79)*, probably via an as-yet unidentified hypothalamic factor *(80,81)*. Ghrelin infusion elicits GH secretion as well as a prolonged increase in circulating SST *(82)*. SST, on the other hand, has been shown to abolish ghrelin-stimulated GH release *(83)*. The exact role of leptin, probably mediated through neuropeptide Y's action on both GHRH and SST neurons *(84,85)*, in the regulation of human GH secretion is not clear at present. GHSs are resistant to several inhibitors of GH secretion such as increased free fatty acids, hyperglycemia, atropine, and increased SST *(86)*. It has recently been suggested that ghrelin secretion from the stomach may be regulated by SST *(87)*. The significant stimulation of GH secretion by ghrelin is partly effected through antagonism of SST activity *(88)*. The neuropeptide cortistatin (CST-14) is highly homologous with SST-14 and binds to all of the SSTRs, resulting in inhibition of basal and GHRH-, or ghrelin-stimulated GH release and insulin secretion, with efficacy equal to that of SST-14 *(89)*. Cortistatin is mainly expressed in the cortex, where it depresses cortical activity. Although it shares many similar functional properties, including depression of neuronal activity, CST is not an alternative SST. Non-SST-type functions include induction of slow-wave sleep, reduced locomotor activity, and possible effects on learning and memory *(88)*.

Hypothalamic control of TSH secretion is modulated by both thyrotropin-releasing hormone (TRH) stimulation and SST inhibition *(6,7)*. Direct inhibition of basal TSH secretion by SST (SST-14 and -28 being equipotent here *[90]*) is associated with a reduction in TSH pulse amplitude (~70%), cessation of the nocturnal TSH surge, and limited reduction in TSH pulse frequency *(91)*. Indirect suppression of TSH secretion occurs through reduction in pituitary thyrotroph TSH receptor numbers *(92)*. SST antagonizes the prosecretory action of TRH on TSH secretion from anterior pituitary thyrotrophs in normal and hypothyroid patients *(93–96)*, and may have a direct inhibitory effect on the secretion of TRH itself from the hyopothalamus *(97,98)*. Hypothyroidism, by downregulating SSTR-2 and SSTR-5, impairs SST's ability to decrease TSH secretion from thyrotrophs *(99)*.

In vitro studies have demonstrated that SST inhibits proliferation of lymphoid, including immune, and hemopoietic cells *(100–102)* as well as influences migration of normal and leukemic hemopoietic stem cells to various specific tissue locations *(103)*. The expression of SSTR-2 and CST, but not SST, in monocyte cell lines suggests that CST may be a possible ligand for SSTR-2, which may then have a regulatory role in the human immune network *(104)*.

Of the lymphatic organs, the thymus has the highest concentration of SST *(105–107)*, with exclusive expression of SSTR-1, -2A and -3. SST appears to be intimately involved in normal thymic function and may have a role to play in both the age-related involution and autoimmune diseases of the thymus *(108,109)*. Within the retina, both SST and SSTR (SSTR-1–5 in selected sites) expression has been demonstrated, and the role of SST as a neuromodulator in the retina has been established *(110,111)*, providing a rationale for the effective use of SST analogs in treating proliferative diabetic retinopathy and macular diseases *(111)*.

Somatostatin Receptors

As already stated, SST mediates its inhibitory effects through binding to specific cell-surface SSTRs that transduce its influence via activation of specific intracellular signaling pathways. Six SSTR subtypes have been identified and characterized: SSTR-1. -2A. -2B. -3. -4. and -5 *(8,112–120)*. They are expressed throughout the body, in several

Table 2
Characteristics of Human SSTRs

	SSTR-1	SSTR-2A	SSTR-3	SSTR-4	SSTR-5
Chromosomal localization	14q13	17q24	22q13.1	20p11.2	16p13.3
Amino acids	391	369	418	388	363
Molecular mass (kDa)	53–72	71–79	65–85	45	52–66
mRNA (kb)	4.8	8.5 (?)	5.0	4.0	4.0
Sequence homology (%)					
SSTR-1	100	43.8	40.6	54.8	43.3
SSTR-2A		100	44.1	41.1	48.5
SSTR-3			100	38.6	52.1
SSTR-4				100	46.3
SSTR-5					100
G protein coupling	+	+	+	+	+
Binding affinities (IC_{50}[n*M*])[a]					
SST-14	1.1–2.26	0.2–1.3	1.4–1.6	0.5–1.8	0.9
SST-28	2.2	4.1	6.1	1.1	0.07
Signal transduction pathway activity[b]					
Adenyl cyclase	↓	↓	↓	↓	↓
Tyrosine phosphatase	↑	↑	↑	↑	
Ca^{2+} channels		↓			
Na^{+}/H^{+}exchanger	↑				
Phospholipase C/IP_3		↑			↑↓
Phospholipase A_2				↑	
MAPK			↓	↑	↓
Tissue distribution	Brain	Brain	Brain	Brain	Brain (±)
	Pituitary	Pituitary	Pituitary	Pituitary (±)	Pituitary
	Stomach	Stomach	Stomach	Stomach	Stomach
	Liver (±)	Liver			
	Pancreas (β-cell)	Pancreas (α-cell)		Pancreas	Pancreas (β, δ-cells)
	Kidney	Kidney			
	Lung	Lung (±)		Lung	Lung (±)
	Intestine	Intestine	Intestine (±)	Intestine (±)	Intestine
	Spleen	Spleen	Spleen	Spleen (±)	Spleen (±)
	Thymus	Thymus	Thymus		
	Uterus (±)	Uterus		Uterus (±)	Uterus (±)
					Placenta (±)
					Adrenal

[a] IC_{50} is the concentration necessary for 50% inhibition of the binding of ^{125}I-labeled SST to cloned subtypes expressed in Chinese hamster ovary or transformed African green monkey COS kidney cells.

IP_3, inositol triphosphate; MAPK, mitogen-activated protein kinase. (Adapted from refs. *8, 124, 133, 138, 139, 174,* and *191*.)

[b] See ref. *125* for further details.

different tissues and cell types, in varying numbers and combinations, with single cells expressing one or several SSTR subtypes at different densities *(6,111,121–125)* (Table 2). Within the anterior pituitary, SSTRs have been demonstrated on the cell membranes of somatotrophs, lactotrophs, thyrotrophs, gonadotrophs and corticotrophs *(121,122,126)*, the most abundant expression being that of SSTR-1, -2, and -5 *(127,128)*. The definitive detection of SSTR-3 *(127)* and SSTR-4 *(127,128)* in the pituitary is not conclusive, possibly owing to either absence or low-level expression. Pituitary adenomas, however, express SSTR-1, -2, -3, and -5 *(127–130)*.

SSTRs are all members of the family of G protein–coupled receptors (GPCRs) characterized by seven α-helical transmembrane–spanning domains, creating three intra-and extracellular loops *(131–133)*. SSTRs interact with several types of Gα. β, γ proteins *(125)* and have also been shown to interact directly with structural cell proteins through their C-terminal domains *(134–136)*. One function of this binding may be to facilitate targeting of SSTRs to the cell sur-

face and elsewhere within the cell. The nonallelic genes coding for each receptor are located on separate chromosomes *(8,103,108,137)* (Table 2), providing for tissue-specific differential expression and exclusive functions in different organs. Besides SSTR-2, the genes are all intronless in their protein-coding sequences *(8,120,124,138,139)*. Alternate splicing of a cryptic intron in the SSTR-2 gene produces two isoforms, which differ in the lengths of their cytoplasmic carboxy termini, SSTR-2A (long) and SSTR-2B (short) *(8,138,140,141)*. SSTR-2A appears to be the predominant physiologically active isoform. Regulation of SSTR gene expression is influenced by glucocorticoids *(142–145)*, sex steroids *(146–148)*, thyroid hormone *(149–151)*, and positively by SST itself *(152)*. Determination of promoter regions and their control is under investigation *(153)*. In rainbow trout, two SSTR-1 genes code for different receptors—SSTR-1A and SSTR-1B (90% homology)—that are differentially expressed in terms of tissue distribution and relative abundance *(154)*.

The different SSTRs exhibit significant sequence homology with each other, ranging on average from 42 to 60% *(8,155–157)*, with SSTR-1 and SSTR-4 being most similar *(155)*. There is also structural conservation of individual subtypes across species *(139,156,157)*. Unique to the SSTRs is a highly conserved amino acid sequence in the seventh transmembrane domain, YANSCANPI/VLY *(8,138)*, which is also found in other species, thus confirming a historic place in evolution.

Following synthesis within the Golgi apparatus, SSTRs are translocated to the surface plasma membrane on the cytoplasmic surface of secretion vesicles *(158)*, which fuse with the cell membrane without vesicle lysis *(159)*. The group of SSTRs has been subdivided on the basis of structural similarities and binding studies using synthetic SST analogs; SSTRs-2, -3, and -5 react with octapeptide (octreotide) and hexapeptide (lanreotide) SST synthetic analogs, while SSTR-1 and SSTR-4 do not *(120)*. This may have clinical relevance in therapeutic decisions.

Each SSTR has specific pharmacologic and physiologic properties *(8,155,160)* (Table 2). All SSTRs bind both SST-14 and SST-28 with high affinity. SSTR-1–4 exhibit higher binding affinity for SST-14 than SST-28, while SSTR-5 has greater selectivity for SST-28 *(8)* (Table 2). However, SST-28 binds to rat pituitary receptors with three times more affinity than SST-14 *(161)*. The ligand-binding sites on SSTRs for SST consist of a "pocket" containing residues within the transmembrane domains III–VII *(162)*, as well as some in the second extracellular domain *(163,164)*. These sites probably vary somewhat between receptors, but the main association of the core conserved SST residues, Phe^{7}, Trp^{8}, Lys^{9}, and Thr^{10} , which constitute a β turn, is with the residues Asn^{276} and Phe^{294} at the outer ends of transmembrane regions VI and VII, respectively. These latter two amino acids are found in SSTR-2 but not SSTR-1. The amino acid Asp^{137} in transmembrane region III anchors the ligand to the receptor through an electrostatic attraction with Lys^{9} *(165)*.

Binding of SST to monomeric cell-surface SSTR-1 and SSTR-5 triggers both homo- and hetero-SSTR dimerization *(166,167)*. This enhances ligand-receptor binding affinity resulting in receptor subtype modification. The functional significance of receptor heterodimerization, restricted to only some SSTRs, varies according to the receptors involved; for example, SSTR-5 forms heterodimers with SSTR-1 but not SSTR-4 *(167)*. SSTR-2A and SSTR-3 form homodimers when expressed separately *(168)*. However, heterodimerization of SSTR-2A and SSTR-3, when coexpressed in HEK 293 cells, results in loss of function of SSTR-3 *(168)*. In addition to this communication between receptor subtypes within the same GPCR family, enhanced functional activity has been demonstrated for the "new receptor" formed by the heterooligomerization of dopamine receptor DR2 and SSTR-5, members of different, but related, GPCRs *(166,169)*. Heterodimerization of SSTR-2A and the μ-opioid receptor (MORI), representatives of closely related GPCR families, in a human embryonic renal cell line did not alter their respective ligand-binding or coupling properties. Binding of this heterodimer to ligands for each of the two receptors separately leads to phosphorylation, internalization, and desensitization of both receptors in the case of SSTR-2A, and phosphorylation and desensitization, but not internalization, of SSTR-2A in the case of the MORI selective ligand *(170)*. These interactions suggest the possibility of many more and make for a highly sophisticated level of fine-tuning of regulation and modulation of intramembrane receptor interactions (including activation/deactivation of GPCRs), hormone-receptor interactions, and cell molecular functional regulation. This includes SSTR subtype selective influence on specific cellular inhibitory effects, such as intracellular phosphorylation of serine and threonine residues which results in GPCR signal termination.

The potential clinical applications have already begun to be explored. Culler et al. *(171)* have demonstrated synergistic suppression (73%) of GHRH stimulated GH secretion from primary fetal pituitary cells using combined SSTR-2 and -5 selective agonists, compared with using these agonists alone (32% for SSTR-2 and 34% for SSTR-5). An SSTR-2 and -5 "biselective" analog demonstrates enhanced suppression of GH hypersecretion by octreotide-resistant acromegalic tumors *(172)*. A hybrid analog molecule, BIM-23A387, with high affinity for both SSTR-2 and D2 has been shown to have an enhanced inhibitory effect on in vitro prolactin (PRL) and GH release from human pituitary adenoma, GH, and GH/PRL-secreting cells. This molecule is far more potent than either SSTR-2 or D2 analogs alone or in combination. The mechanism for this awaits explanation *(173)*.

The physiologic actions of SST are most likely both SSTR subtype specific and the result of the interaction of two or more SSTRs within a given cell membrane following SST ligand binding. The identification and elucidation

of the intracellular signal transduction pathways following SST/SSTR binding have been derived mainly from in vitro cell transfection studies *(125)*. The common effect is a reduction in intracellular cyclic adenosine monophosphate (cAMP) and Ca^{2+} with activation of protein phosphatases. The final pathway, and hence effect on cellular function, will vary, depending on the specific SSTR subtype and SST ligand involved. Inhibition of cell secretion may be achieved through four main intracellular effector pathways *(174)*: (1) inhibition of adenyl cyclase, with a fall in intracellular cAMP *(133, 175,176)*, a functional coupling existing for all SSTRs; (2) reduction in intracellular Ca^{2+}, resulting from a fall in transmembrane Ca^{2+} influx, owing to activation and hyperpolarization of several K^+ and voltage-dependent Ca^{2+} channels *(174)*; (3) activation of protein phosphatases (calcineurin specifically inhibiting exocytosis *[177]*) and serine/threonine phosphatases *(178)*, which influence Ca^{2+} and K^+ channels; (4) activation of intracellular tyrosine phosphatase *(179–181)*, which, through different cascades, inhibits cellular proliferation (G1 cell-cycle arrest following SSTR-1, -2, -4, and -5 stimulation of the mitogen-activated protein kinase pathway) *(180,182–184)* and promotes apoptosis, exclusively via the "cytotoxic" SSTR-3 *(139,185–189)*. The antiproliferative action of SST may also be responsible for tumor shrinkage *(190)*, as may inhibition of angiogenesis and immune modulation *(191)* by SST. Direct SST inhibition of growth-promoting factors and hormones constitutes an additional antiproliferative mechanism. Cell-cycle regulation by SSTR is both subtype specific—SSTR-5 and SSTR-2 inhibiting cell growth by 80 and 60% respectively—and agonist dependent, with cell-cycle arrest occurring in the S phase *(192)*.

Using models of SSTR inhibition, including knockout animal models and antisense oligonucleotides, it has been demonstrated that SSTR-1 is involved in regulating basal GH secretion from pituitary somatotrophs *(193)*, as well as influencing GH pulse amplitude at the hypothalamic level *(194)*. The inhibition of gastric acid secretion is mediated through SSTR-2 inhibition of gastrin activity *(195)*. SST inhibition of GH and TSH secretion is mediated through SSTR-2 and/or SSTR-5 *(196,197)* in primary human fetal pituitary cell cultures from somatotrophs and thyrotrophs, respectively. Enhanced inhibition has been demonstrated in primary cell cultures from human GH–secreting pituitary somatotroph tumors when both SSTR-2 and -5 are activated simultaneously by the same ligand *(198)*. Physiologic suppression of PRL secretion is mediated by SSTR-2 in human fetal pituitary cell cultures *(186,198)*, whereas SSTR-5 modulates PRL suppression in prolactinomas *(198)*. Inhibition of glucagon secretion from pancreatic α-cells is mediated through SSTR-2, while SSTR-5, present on more than 80% of β-cells, reduces insulin secretion from these pancreatic β-cells *(197,199–204)*. The demonstration that SSTR-1 modulates antiangiogenic activity through suppression of endothelial sprouting in vitro leads the way to exploiting this in the treatment of proliferative diseases involving angiogenesis *(205)*.

Tolerance to continued exposure to SST results in SSTR downregulation in most tissues, with a decline in the specific initial response *(124)*. This does not hold true in the case of inhibition of gallbladder motility, presumably owing to a different set of SSTRs in the gallbladder wall. Persistently elevated levels of SST or analogs result in an increased incidence of gallbladder sludge and gallstones *(124)*. Most hormone-secreting tumors, which generally express a high density of SSTRs (e.g., GH adenomas, carcinoids, VIPomas), do not experience desensitization to chronic SST exposure *(139)* resulting in persistent suppression of hormone secretion. SSTR physiology is subtype specific, and SST regulation of its receptors *(139)* is seen in studies with SST analogs administered for short (15–90 min) and prolonged (24–48 h) periods of time, demonstrating upregulation of SSTR-1 *(206)* and SSTR-2, and cellular internalization of subtypes 3 and 5 *(206,207)*. SSTR-2 is rapidly internalized following ligand binding, while SSTR-5 undergoes recycling with recruitment of stored SSTR-5 soon after internalization *(208)*. Termination of agonist activity occurs through the mechanism of SSTR desensitization: intracellular receptor phosphorylation, uncoupling from G proteins, internalization (subtype specific, using SSTR-transfected CHO-K1 cells; SSTR-3 [78%], SSTR-5 [66%], SSTR-4 [29%], SSTR-1 [0%] *[207]*), and degradation *(125,209–211)*. These effects can be exploited clinically, in diagnostic receptor scanning and targeted radiotherapy, respectively.

Conclusion

The pervasive endocrine inhibitory hormone, SST, plays a crucial role in the physiology of GH secretion as well as influencing nervous system and GI endocrine and exocrine functions. Its role in endocrine and other diseases remains to be defined. Appreciation of the factors involved in the regulation of SSTR status as well as in the control of tissue-specific SSTR expression will play an increasingly important role in the search for improved medical therapeutic options. Recognition of the expression of several SSTRs on single cells as well as the relationship to other related cell-surface receptors will promote the development of novel therapies. The expression of SST receptors on pituitary tumors, hormone-secreting tumors (carcinoids, insulinomas, glucagonomas, and pheochromocytomas *[212–214]*), and many different cancers is already being exploited clinically in the fields of diagnosis and therapy *(215,216)*. New synthetic SSTR subtype–specific and universally binding peptide and nonpeptide agonists and antagonists are enhancing the therapeutic arsenal for the management of these diseases.

References

1. Krulich, L., Dhariwal, A. P. S., and McCann, S. M. (1968). *Endocrinology* **83,** 783–790.
2. Brazeau, P., Vale, W. W., Burgus, R., et al. (1973). *Science* **179,** 77–79.
3. Pelletier, G., Dube, D., and Puviani, R. (1977). *Science* **96,** 1469–1470.
4. Lamberts, S. W. J. (1988). *Endocr. Rev.* **9,** 417–436.
5. Lamberts, S. W. J., Krenning, E. P., and Reubi, J. C. (1991). *Endocr. Rev.* **12,** 450–482.
6. Reichlin, S. (1983). *N. Engl. J. Med.* **309,** 1495–1501.
7. Reichlin, S. (1983). *N. Engl. J. Med.* **309,** 1556–1563.
8. Reisine, T. and Bell, G. I. (1995). *Endocr. Rev.* **16,** 427–442.
9. Pradayrol, L., Jornvall, H., Mutt, V., and Ribet, A. (1980). *FEBS Lett.* **109,** 55–58.
10. Shen, L. P., Picket, R. L., and Rutter, W. J. (1982). *Proc. Natl. Acad. Sci. USA* **79,** 4575–4579.
11. Urman, S. and Critchlow, V. (1983). *Endocrinology* **112,** 659–664.
12. Chihara, K., Arimura, A., and Schally, A. V. (1979). *Endocrinology* **104,** 1659–1664.
13. Miller, R. P., Sheward, R. J., Wegener, I., and Rink, C. (1983). *Brain Res.* **260,** 334–338.
14. Peters, G. E. (1982). *Regul. Pept.* **3,** 361–369.
15. Bugnon, C., Fellmann, D., and Bloch, B. (1978). *Metabolism* **27,** 1161–1165.
16. Ackland, J., Ratter, S., Bourne, G. L., et al. (1983). *Regul. Pept.* **5,** 95–101.
17. Bresson, J.-L., Clavequin, M.-C., Fellmann, D., et al. (1984). *Neuroendocrinology* **39,** 68–73.
18. Elde, R. P. and Parsons, J. A. (1975). *Am. J. Anat.* **144,** 541–548.
19. Desy, L. and Pelletier, G. (1977). *Cell Tissue Res.* **184,** 491–497.
20. Finley, J. C. W., Maderhut, J. L., Roger, L. J., et al. (1981). *Neuroscience* **6,** 2173–2192.
21. Johanson, O., Hokfelt, T., and Elde, R. P. (1984). *Neuroscience* **13,** 265–339.
22. Levy, L., Bourdais, J., Mouhieddine, B., et al. (1993). *J. Clin. Endocrinol. Metab.***76,** 85–90.
23. Hokfelt, T., Efendic, S., Hellerstrom, C., et al. (1975). *Acta Endocrinol.* **80(Suppl. 200),** 5–41.
24. Polak, J. M., Pearse, A. G. E., Grimelius, L., et al. (1975). *Lancet* **1,** 1220–1222.
25. Orci, L., Beatens, D., Dubois, M. P., et al. (1975). *Horm. Metab. Res.***7,** 400–402.
26. Rufener, C., Dubois, M. P., Malaisse–Lagae, F., et al. (1975). *Diabetologica* **11,** 321–324.
27. Tannenbaum, G. S. and Ling, N. (1984). *Endocrinology* **115,** 1952–1957.
28. Borbely, A. A. and Tobler, I. (1989). *Physiol. Rev.* **69(2),** 605–670.
29. Barinaga, M., Bilezikjian, L. M., Vale, W. W., et al. (1985). *Nature* **314,** 279–281.
30. Musseo, M., Tiengso, A., Fedele, D., and Crepaldi, G. (1979). *Arch. Intern. Med.* **139,** 1157–1160.
31. Vance, M. L., Kaiser, D. L., Martha, P. M. Jr., et al. (1989). *J. Clin. Endocrinol. Metab.* **68,** 22–28.
32. Hindmarsh, P. C., Brain, C. E., Robinson, I. C. A. F., Matthew, D. R., and Brook, C. G. D. (1991). *Clin. Endocrinol.* **35,** 353–360.
33. Degli Aberti, E. C., Ambrosio, M. R., Cella, S. G., et al. (1997). *J. Clin. Endocrinol. Metab.* **82,** 2885–2888.
34. Tzanella, M., Guyda, H., Van Vliet, G., and Tannenbaum, G. S. (1996). *J. Clin. Endocrinol. Metab.* **81,** 2487–2494.
35. Guillemin, R. (1978). *Science* **202,** 390–402.
36. Tannenbaum, G. S., Painson, J. C., Lengyel, A. M. J., et al. (1989). *Endocrinology* **124,** 1380–1388.
37. Stachura, M. E., Tyler, J. M., and Farmer, P. K. (1988). *Endocrinology* **123,** 1476–1482.
38. Kraicer, J., Sheppard, M. S., Luke, J., Lussier, B., Moor, B. C., and Cowan, J. S. (1988). *Endocrinology* **122,** 1810–1815.
39. Kelijman, M. and Frohman, L. A. (1990). *J. Clin. Endocrinol. Metab.* **71,** 157–163.
40. Dieguez, C. and Casanueva, F. F. (1995). *Trends Endocrinol. Metab.* **6,** 55–59.
41. Kanaley, J. A., Weatherup-Dentes, M. M., Jaynes, E. B., and Hartman, M. L. (1999). *J. Clin. Endocrinol. Metab.* **84,** 3156–3161.
42. Cordido, F., Casanueva, F. F., and Dieguez, C. (1989). *J. Clin. Endocrinol. Metab.* **68,** 290–293.
43. Andreotti, A. C., Lanzi, R., Manzoni, M. F., Caumo, A., Moreschi, A., and Pontiroli, A. E. (1994). *Metabolism* **43,** 1207–1213.
44. Cordido, F., Peino, R., Penalva, A., Alvarez, C. V., Casanueva, F. F., and Dieguez, C. (1996). *J. Clin. Endocrinol. Metab.* **81,** 914–918.
45. Maccario M., Procopio M., Grottoli S., et al. (1996). *Metabolism* **45,** 342–346.
46. Alvarez, P., Isidro, L., Leal-Cerro, A., Casanueva, F. F., Dieguez, C., and Cordido, F. (2002). *Clin. Endocrinol.* **56(4),** 487–492.
47. Herman, V., Weiss, M., Becker, D., and Melmed S. (1990). *Endocr. Pathol.* **1,** 236–244.
48. Barinaga, M., Yamanoto, G., Rivier, G., et al. (1983). *Nature* **306,** 84–86.
49. Fukata, J., Diamond, D. J., and Martin, J. B. (1985). *Endocrinology* **117,** 457–467.
50. Chihara, K., Arimura, A., and Schally, A. V. (1979). *Endocrinology* **104,** 1656–1662.
51. Berelowitz, M., Dudlak, D., and Frohman, L. A. (1982). *J. Clin. Invest.* **69,** 1293–1301.
52. Ross, R. J. M., Borges, F., Grossman, A., et al. (1987). *Clin. Endocrinol.* **26,** 117–123.
53. Sheppard, M. C., Kronheim, S., and Pimstone, B. L. (1978). *Clin. Endocrinol.* **9,** 583–586.
54. Rosenthal, S. M., Hulse, J. A., Kaplan, S. L., and Grumbach, M. M. (1986). *J. Clin. Invest.* **77,** 176–180.
55. Bilezikjan, L. M. and Vale, W. W. (1984). *Endocrinology* **115,** 2032–2034.
56. Davis, J. R. E., Sheppard, M. C., Shakespear, R. A., et al. (1986). *Clin. Endocrinol.* **24,** 135–140.
57. Bilezikjian, L. M., Seifert, H., and Vale, W. (1986). *Endocrinology* **118,** 2045–2052.
58. Peterfreund, R. A. and Vale, W. W. (1984). *Neuroendocrinology* **39,** 397–402.
59. Aguila, M. C. and McCann, S. M. (1985). *Endocrinology* **117,** 762–765.
60. Koerker, D. J., Rutch, W., Chideckel, E., et al. (1974). *Science* **184,** 482–484.
61. Yamashita, S., Weiss, M., and Melmed, S. (1986). *J. Clin. Endocrinol. Metab.* **63,** 730–735.
62. Yamashita, S. and Melmed, S. (1986). *Endocrinology* **118,** 176–182.
63. Berelowitz, M., Szabo, M., Frohman, L. A., et al. (1982). *Science* **212,** 1279–1281.
64. Howe, N. M. and Sheridan, M. A. (2002). Endocrine Society's 84th Annual Meeting, P3-271.
65. Nakamura, S., Mizuno, M., Kataami, H., and Terasawa, E. (2002). Endocrine Society's 84th Annual Meeting, OR-44-4.
66. Horvath, S., Palkovits, M., Gorcs, T., et al. (1989). *Brain Res.* **481,** 8–15.
67. Cuttler, L. (1996). *Endocrinol. Metab. Clin. North Am.* **25,** 541–571.
68. Giustina, A. and Veldhuis, J. D. (1998). *Endocr. Rev.* **19,** 717–797.

69. Dieugez, C. and Casanueva, F. F. (2000). *Eur. J. Endocrinol.* **142,** 535–541.
70. Schonbrunn A., Liu Q., Elberg G., et al. (2002). Endocrine Society's 84th Annual Meeting, L6-1.
71. Chihara, K., Minamitani, N., Kaji, H., et al. (1984). *Endocrinology* **114,** 1402–1406.
72. Chihara, K., Kodama, H., Hidesuke, K., et al. (1985). *J. Clin. Endocrinol. Metab.* **61,** 229–233.
73. Terry, L. C., Crowley, W. R., Lynch, C., et al. (1982). *Peptides* **3,** 311–318.
74. Goth, M. I., Lyons, C. E., Canny, B. J., and Thomer, M. O. (1992). *Endocrinology* **130,** 939–944.
75. Jaffe, C. A., Ho, P. J., Demott, F. R., et al. (1993). *J. Clin. Endocrinol. Metab.* **77,** 1641–1647.
76. Penalva, A., Carballo, A., Pombo, M., et al. (1993). *J. Clin. Endocrinol. Metab.* **76,** 168–171.
77. Guillaume, V., Magnan, E., Cataldi, M., et al.. (1994). *Endocrinology* **135,** 1073–1076.
78. Yagi, H., Kaji, H., Sato, M., et al. (1996). *Neuroendocrinology* **63,** 198–206.
79. Arvat, E., Gianotti, L., Di Vito, L., et al. (1995). *Neuroendocrinology* **61,** 51–56.
80. Popovic, V., Damjanovic, S., Micic, D., et al. (1995). *J. Clin. Endocrinol. Metab.* **80,** 942–947.
81. Bowers, C. Y., Sartor, A. A., Reynolds, D. G., and Badger, T. A. M. (1991). *Endocrinology* **128,** 2027–2035.
82. Arosio, M., Cappiello, V., Manenti, S., et al. (2002). Endocrine Society 84th Annual Meeting, OR58-4.
83. Malagon, M. M., Ruiz-Guerero, E., Luque, R. M., et al. (2002). Endocrine Society 84th Annual Meeting, P2-113.
84. Carro, E., Senaris, R., Considine, R. V., Casanueva, F. F., and Dieguez, C. (1998). In: *Proceedings of the IVth European Congress of Endocrinology.* Seville, Spain, P1-261 (Abstract).
85. Carro, E., Seoane, L. M., Senaris, R., Considine, R. V., Casanueva, F. F., and Dieguez, C. (1998). *Neuroendocrinology* **66,** 375–377.
86. Ghigo, E., Arvat, E., Muccioli, G., and Camanni, F. (1997). *Eur. J. Endocrinol.* **136,** 445–460.
87. Katakami, H., Yamada, S., Sanno, N., et al. (2002). Endocrine Society 84th Annual Meeting, P3-543.
88. Spier, A. D. and de Lecea, L. (2000). *Brain Res. Rev.* **33,** 228–241.
89. Broglio, F., Arvat, E., and Benso, A., et al. (2002). *J. Clin. Endocrinol. Metab.* **87(8),** 3783–3790.
90. Rodriguez-Arnao, M. D., Gomez-Pan, A., Rainbow, S. J., et al. (1981). *Lancet* **1(8216),** 353–356.
91. Samuels, M. H., Henry, P., and Ridgway, E. C. (1992). *J. Clin. Endocrinol. Metab.* **74,** 217–222.
92. Lewis, B. M., Dieguez, C., Ham, J., et al. (1989). *J. Neuroendocrinol.* **1,** 437–442.
93. Arima, A. and Schally, A. V. (1976). *Endocrinology* **98,** 1069–1075.
94. Ferland, L., Labrie, F., Jobin, M., et al. (1976). *Biochem. Biophys. Res. Commun.* **68,** 149–156.
95. Tanjasiri, P., Kozbur, X., and Florsheim, W. H. (1976). *Life Sci.* **19,** 657–661.
96. Stockigt, J. R. (2002). In: *Werner and Ingbar's the thyroid, a fundamental and clinical text, 8th ed.* Braverman, L. E. and Utiger, R. D. (eds.). JB Lippincott: Philadelphia.
97. Vale, W., Brazeau, P., Rivier C., et al. (1975). *Recent Prog. Horm. Res.* **31,** 365–397.
98. Siler, T. M., Yen, S. S. C., Vale, W., and Guillemin, R. (1974). *J. Clin. Endocrinol. Metab.* **38,** 742–747.
99. James, R. A., Sarapura, V. D., Bruns, C., et al. (1997). *Endocrinology* **138,** 719–724.
100. Van Hagen, P. M., Krenning, E. P., Kwekkeboom, D. J., et al. (1994). *Eur. J. Clin. Invest.* **24,** 91–99.
101. Ferone, D., van Hagen, P. M., van Koetsveld, P. M., et al. (1999). *Endocrinology* **140,** 373–380.
102. Lamberts, S. W. J., van der Lely, A. J., and Hofland, L. J. (2000). *Eur. J. Endocrinol.* **143,** 701–705.
103. Oomen, S. P. M. A., Hofland, L. J., van Hagen, P. M., Lamberts, S. W. J., and Touw, I. P. (1994). *Eur. J. Endocrinol.* **143,** 9–14.
104. Dalm, V. A. S. H., van Hagen, M., van Koetsveld, P. M., van der Lely, A. J., Lamberts, S. W. J., and Hofland, L. J. (2002). Endocrine Society's 84th Annual Meeting, P2-265.
105. Fuller, P. J. and Verity, K. (1989). *J. Immunol.* **143,** 1015–1017.
106. Aguila, M. C., Dees, W. L., Haensly, W. E., and McCann, S. M. (1991). *PNAS* **88,** 11485–11489.
107. Stanisz, A. M., Befus, D., and Bienenstick, J. (1986). *J. Immunol.* **136,** 152–156.
108. Ferone, D., van Hagen, P. M., Pivonello, R., Colao A., Lamberts, S. W. J., and Hofland, L. J. (2000). *Eur. J. Endocrinol.* **143,** 27–34.
109. Ferone, D., Pivonello, R., van Hagen, M. P., et al. (2002). Endocrine Society's 84th Annual Meeting, P2-266.
110. Zalutsky, R. A. and Miller, R. F. (1990). *J. Neurosci.* **10,** 383–393.
111. van Hagen, P. M., Baarsma, G. S., Mooy, C. M., et al. (2000). *Eur. J. Endocrinol.* **143,** 43–51.
112. Yamada, Y., Post, S. R., Wang, K., Tager, H. S., Bell, G. I., and Seino, S. (1992). *PNAS* **89,** 251–255.
113. Yamada, Y., Reisine, T., Law, S. F., et al. (1992). *Mol. Endocrinol.* **6,** 2136–2142.
114. Bruno, J. F., Xu, Y., Song, J., and Berelowitz, M. (1992). *Proc. Natl. Acad. Sci. USA* **89,** 11151–11155.
115. O'Carroll, A. M., Lolait, S. J., Konig, M., and Mahan, L. C. (1992). *Mol. Pharmacol.* **42,** 939–946.
116. Roher, L., Raulf, F., Bruns, C., Buettner, R., Hofstaedter, F., and Schule, R. (1993). *Proc. Natl. Acad. Sci. USA* **90,** 4196–4200.
117. Panetta, R. and Patel, Y. C. (1995). *Life Sci.* **56,** 333–342.
118. Patel, Y. C., Greenwood, M. T., Panetta, R., Demchyshyn, L., Niznik, H., and Srikant, C. B. (1995). *Life Sci.* **57,** 1249–1265.
119. Patel, Y. C. (1997). *J. Endocrinol. Invest.* **20,** 348–367.
120. Hoyer, D., Bell, G. I., Berelowitz, M., et al. (1995). *Trends Pharmacol. Sci.* **16,** 86–88.
121. Day, R., Dong, R., Panetta, J., Kraicer, M. T., Greenwood, M. T., and Patel, Y. C. (1995). *Endocrinology* **136,** 5232–5235.
122. O'Carroll, A. M. and Krempels, K. (1995). *Endocrinology* **136,** 5224–5227.
123. Kumer, U., Laird, D., Srikant, C., et al. (1997). *Endocrinology* **138,** 4473–4476.
124. Lamberts, S. W., van der Lely, A. J., de Herder, W. W., and Hofland, L. J. (1996). *N. Engl. J. Med.* **334,** 246–254.
125. Csaba, Z. and Dournaud, P. (2001). *Neuropeptides* **35(1),** 1–23.
126. Morel, G., Leroux, P., and Pelletier, G. (1985). *Endocrinology* **116,** 1615–1620.
127. Miller, G. M., Alexander, J. M., Bikkal, H. A., Katznelson, L., Zervas, N. T., and Klibanski, A. (1995). *J. Clin. Endocrinol. Metab.* **80,** 1386–1392.
128. Panetta, R., Greenwood, M. T., Warsznska, A., et al. (1994). *Mol. Pharmacol.* 417–427.
129. Greenman, Y. and Melmed, S. (1994). *J. Clin. Endocrinol Metab.* **78,** 398–403.
130. Greenman, Y. and Melmed, S. (1994). *J. Clin. Endocrinol. Metab.* **79,** 724–729.
131. Yasuda, K., Rens-Domiano, S., Breder, C. D., et al. (1992). *J. Biol. Chem.* **267,** 20422–20428.
132. Raynor, K., Murphy, W. A., Coy, D. H., et al. (1993). *Mol. Pharmacol.* **43,** 838–844.
133. Patel, Y. C. and Srikant, C. B. (1994). *Endocrinology* **135,** 2814–2817.

134. Zitzer, H., Honck, H. H., Bachner, D., Richter, D., and Kreienkamp, H. J. (1999). *J. Biol. Chem.* **274,** 32997–33001.
135. Zitzer, H., Richter, D., and Kreinkamp, H. J. (1999). *J. Biol. Chem.* **274,** 18153–18156.
136. Schwarzler, A., Kreinekamp, H. J., and Richter, D. (2000). *J. Biol. Chem.* **275,** 9557–9562.
137. Bruns, C., Shi, V., Hoyer, D., Schuurman, H., and Weckbecker, G. (2000). *Eur. J. Endocrinol.* **143,** 53–57.
138. Patel, Y. C., Greenwood, M. T., Panetta, R., Demchyshyn, L. L., Niznick, M. B, and Srikant, C.B. (1995). *Life Sci.* **57,** 1249–1265.
139. Patel, Y. C. (1997). *J. Endocrinol. Invest.* **20,** 345–367.
140. Vanetti, M., Kouba, M., Wang, X., Vogt, G., and Hollt, V. (1992). *FEBS Lett.* **311,** 290–294.
141. Reisine, T., Kong, H., Raynor, K., et al. (1993). *Mol. Pharmacol.* **44,** 1016–1020.
142. Kraus, J., Woltje, M., and Hollt, V. (1999). *FEBS Lett.* **459,** 200–204.
143. Petersenn, S., Rasch, A. C., Presch, S., Beil, F. U., and Schulte, H. M. (1999). *Mol. Cell. Endocrinol.* **157,** 75–85.
144. Xu, Y., Berelowitz, M., and Bruno, J. F. (1995). *Endocrinology* **136,** 5070–5075.
145. Park, S., Kamegai, J., and Kineman, R. D. (2002). Endocrine Society's 84th Annual Meeting, P2-45.
146. Xu, Y., Song, J., Berelowitz, M., and Bruno J. F. (1996). *Endocrinology* **137,** 5634–5640.
147. Xu, Y., Berelowitz, M., and Bruno, J. F. (1998). *Mol. Cell. Endocrinol.* **139,** 71–77.
148. Kimura, K., Tomizawa, S., Arai, K. N., and Kimura, N. (1998). *Endocrinology* **139,** 1573–1580.
149. James, R. A., Sarapura, V. D., Bruns, C., et al. (1997). *Endocrinology* 138, 719–724.
150. Lan, K. S. L. and Wong, R. L. C. (1999). *Neuroendocrinology* **69,** 460–464.
151. Woodmansee, W. W., Gordon, D. F., Dowding, J. M., et al. (2000). *Thyroid* **10,** 533–541.
152. Bruno, J. F., Xu, Y., and Berelowitz, M. (1994). *Biochem. Biophys. Res. Commun.* **202,** 1738–1743.
153. Woodmansee, W. W., Mouser, R. L., Gordon, D. F., et al. (2002). *Endocrinology* **143(6),** 2268–2276.
154. Sheridan, M. and Slagter, B. J. (2002). Endocrine Society's 84th Annual Meeting, P1-476.
155. Yamada, Y., Kagimoto, S., Kubota, A., et al. (1993). *Biochem. Biophys. Res. Commun.* **195,** 844–852.
156. Bruno, J. F., Xu, Y., Song, J., and Berelowitz, M. (1992). *Proc. Natl. Acad. Sci. USA* **89,** 11151–11155.
157. O'Carroll, A. M., Lolait, S. J., Konig, M., and Mahan, L. C. (1992). *Mol. Phamacol.* **42,** 939–946.
158. Draznin, B., Mehler, P. S., Leiter, W., et al. (1985). *J. Receptor Res.* **5(1),** 83–103.
159. Sussman, K. E., Pollard, H. B., Leiter, J. W., Neshers, R., Adler, J., and Cerasi, E. (1983). *Biochem. J.* **214,** 225–230.
160. Rens-Domiano, S., Law, S. F., Yamada, Y., Seino, S., Bell, G. I., and Reisine, T. (1992). *Mol. Pharmacol.* **42,** 28–34.
161. Srikant, C. B. and Patel, Y. C. (1981). *Nature* **294,** 259–260.
162. Kaupman, K., Bruns, C., Raulf, F., Weber, H. P., Mattes, H., and Lubbert, H. (1995). *EMBO J.* **14,** 727–735.
163. Greenwood, M. T., Hukovic, N., Kumar, U., et al. (1997). *Mol. Pharmacol.* **52,** 807–814.
164. Schwartz, T.W. and Rosenkilde, M. M. (1996). *Trends Pharmacol. Sci.***17,** 213–216.
165. Nehring, R. B., Meyerhof, W., and Richter, D. (1995). *DNA Cell Biol.* **14,** 939–944.
166. Rocheville, M., Lange, D. C., Kumar, U., Patel, S. C., Patel, R. C., and Patel, Y. C. (2000). *Science* **288,** 154–157.
167. Rocheville, M., Lange, D. C., Kumar, U., Sasi, R., Patel, R. C., and Patel, Y. C. (2000). *J Biol. Chem.* **275,** 7862–7869.
168. Pfeiffer, M., Koch, T., Schroder, H., et al. (2001). *J. Biol. Chem.* **276,** 14027–14036.
169. Devi, L. A. (2000). *Trends Pharmacol. Sci.* **21,** 324–326.
170. Pfeiffer, M., Koch, T., Schroder, H., Laugsch, M., Hollt, V., and Schultz, S. (2002). *J. Biol. Chem.* **277(22),** 19762–19772.
171. Culler, M. D., Gordon, T., Taylor, J., et al. (2000). Endocrine Society's 82nd Annual Meeting, Toronto, Canada, Abs. 1941.
172. Saveanu, A., Gunz, G., Dufour, H., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 140–145.
173. Saveanu, A., Lavaque, E. D., Gunz, G., et al. (2002). Endocrine Society's 84th Annual Meeting, P2-105.
174. Petersenn, S. (2000). In: *Hormone action, basic and clinical aspects.* Melmed S. (ed.). Bioscientifica Ltd., Bristol, pp. 43–61.
175. Bilezikjian, L. M. and Vale, W. W. (1983). *Endocrinology* **113,** 1726–1731.
176. Schindler, M., Humphrey, P. P. A., and Emson, P. C. (1996). *Prog. Neurobiol.* **50,** 9–47.
177. Renstrom, E., Ding, W. G., Bokvist, K., and Rorsman, P. (1996). *Neuron* **17,** 513–522.
178. White, R. E., Schonbrunn, A., and Armstrong, D. L. (1991). *Nature* **351,** 570–573.
179. Florio, T., Rim, C., Hershberger, R. E., Loda, M., and Stork, P. J. (1994). *Mol. Endocrinol.* **8,** 1289–1297.
180. Buscail, L., Esteve, J.-P., Saint-Laurent, N., et al. (1995). *PNAS* **92,** 1580–1584.
181. Reardon, D. B., Wood, S. L., Brautigan, D. L., Bell, G. I., Dent, P., and Sturgill, T. W. (1996). *Biochem. J.* **314,** 401–404.
182. Viguerie, N., Tahiri-Jouti, N., Ayral, A. M., et al. (1989). *Endocrinology* **124,** 1017–1025.
183. Liebow, C., Reilly, C., Serrano, M., and Schally, A. V. (1989). *PNAS* **86,** 2003–2007.
184. Sharma, K., Patel, Y. C., and Srikant, C. B. (1999). *Mol. Endocrinol.* **13,** 82–90.
185. Sharma, K., Patel, Y. C., and Srikant, C. B. (1996). *Mol. Endocrinol.* **10,** 1688–1696.
186. Rohrer, S., Birzin, E., Mosley, R., et al. (1998). *Science* **282,** 737–740.
187. Srikant, C. B. (1995). *Biochem. Biophys. Res. Commun.* **209,** 400–406.
188. Pagliacci, M. C., Tognellini, R., Grignani F., and Nicoletti, I. (1991). *Endocrinology* **129,** 2555–2562.
189. Cheung, N. W. and Boyages, S. C. (1995). *Endcocrinology* **136,** 4174–4181.
190. Weckbecker, G., Raulf, F., Stolz, B., and Burns, C. (1993). *Pharmacol. Ther.* **60,** 245–264.
191. Patel, Y. C. (1999). *Front. Neuroendocrinol.* **20,** 157–198.
192. Wang, X., Davis, B. K., Levy, S., et al. (2002). Endocrine Society's 84th Annual Meeting, P2-133.
193. Kreienkamp, H. J., Akgun, E., Baumeister, H., Meyerhof ,W., and Richter, D. (1999). *FEBS Lett.* **462,** 464–466.
194. Laneau, C., Bluet-Pajot, M. T., Zizzari, P., et al. (2000). *Endocrinology* **141,** 967–979.
195. Martinez, V., Curi, A. P., Torkian, B., et al. (1998). *Gastroenterology* **114,** 1125–1132.
196. Shimon, I., Taylor, J. E., Dong, J. Z., et al. (1997). *J. Clin. Invest.* **99,** 789–798.
197. Siler, T. M., Yen, S. S. C., Vale, W., and Guillemin, R. (1974). *J. Clin. Endocrinol. Metab.* **38,** 742–745.
198. Shimon, I., Yan, X., Taylor, J. E., Weiss, M. H., Culler, M. D., and Melmed, S. (1997). *J. Clin. Invest.* **100,** 2386–2392.
199. Rossowski, W. J. and Coy, D. H. (1994). *Biochem. Biophys. Res. Commun.* **205,** 341–346.
200. Koerker, D. J., Ruch, W., Chideckel, E., et al. (1974). *Science* **184,** 482–484.
201. Mandarino, L. D., Stenner, W., Blanchard, S., et al. (1981). *Nature* **291,** 76–77.

202. Mitra, S., Mezey, E., Hunyady, B., et al. (1999). *Endocrinology* **149,** 3970–3796.
203. Zambre, Y., Ling, Z., Chen M., et al. (1999). *Biochem. Pharmacol.* **57,** 1159–1164.
204. Fagan, S., Azizzadeh, A., Moldovan, S., et al. (1998). *Surgery* **124,** 254–259.
205. Bocci, G., Culler, M. D., Taylor J. E., et al. (2002). Endocrine Society's 84th Annual Meeting, OR54-4.
206. Hukovic, N., Rocheville, M., Kumar, U., Sasi, R., Khare, S., and Patel, Y. C. (1999). *J. Biol. Chem.* **274,** 24550–24558.
207. Hukovic, N., Panetta, R., Kumar, U., and Patel, Y. C. (1996). *Endcocrinology* **137,** 4046–4049.
208. Stroh, T., Jackson, A. C., Sarret, P., et al. (2000). *Endocrinology* **141,** 354–365.
209. Reisine, T. and Axelrod, J. (1983). *Endocrinology* **113,** 811–813.
210. Reisine, T. (1984). *J. Pharm. Exp. Ther.* **229,** 14–20.
211. Wang, H. L., Dichter, M., and Resine, T. (1990). *Mol. Pharmacol.* **38,** 357–361.
212. Vikic-Topic, S., Raisch, K. P., Kvols, L. K., and Vuk-Pavlovic, S. (1995). *J. Clin. Endocrinol. Metab.* **80,** 2974–2979.
213. Kubota, A., Yamada, Y., Kagimoto, S., et al. (1994). *SMS* **93,** 1321–1325.
214. Epelbaum, J., Bertherat, J., Prevost, G., et al. (1995). *J. Clin. Endocrinol. Metab.* **80,** 1837–1844.
215. Reubi, J. C., Kvols, L., Krenning, E., and Lamberts, S. W. J. (1990). *Metabolism* **39(Suppl. 2),** 78–81.
216. Reubi, J. C., Waser, B., Horisberger, U., et al. (1993). *Blood* **82,** 2143–2151.