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REVIEW ARTICLE

A poles apart applications of somatostatin hormone

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Abstract: Somatostatin is a 14 amino acid peptide that inhibits pancreatic exocrine and endocrine secretion. Initially isolated from the ovine hypothalamus, it is widely distributed throughout the gastrointestinal tract where it may act as a hormone, local chemical messenger, or neurotransmitter to elicit many physiological actions includeing modulation of neurotransmission, inhibition of endocrine secretion, inhibition of cell proliferation and smooth muscles contractility. Its clinical applications have been limited by its very short half-life, necessitating continuous intravenous infusion. Synthethic somatostatin analogs have longer half-lives than somatostatin, but have similar activities. The recent advances in this field will be briefly summarized.

Key words: Somatostain, Receptors, Analogs, Inhibition, Endocrine system

INTRODUCTION:

Hormones are chemicals released by cells that affect cells in other parts of the body. Only a small amount of hormone is required to alter cell metabolism. It is essentially a chemical messenger that transports a signal from one cell to another. All multicellular organisms produce hormones; plant hormones are also called phytohormones. Hormones in animals are often transported in the blood. Cells respond to a hormone when they express a specific receptor for that hormone. The hormone binds to the receptor protein, resulting in the activation of a signal transduction mechanism that ultimately leads to cell type-specific responses.

Endocrine hormones are secreted (released) directly into the bloodstream, while exocrine hormones (or ectohormones) are secreted directly into a duct, and from the duct they either flow into the bloodstream or they flow from cell to cell by diffusion in a process known as paracrine signalling.

The endocrine system is a complex system of glands that produce and secrete hormones directly into the circulatory system to influence, regulate and control metabolism and many of the body's processes.

1.1. Classification of Hormones 2, 3

A) Based on the chemical nature

The hormones can be classified into three groups –

- Protein or peptide hormones: e.g., insulin, antidiuretic hormone (ADH), oxytocin, glucagon etc.
- Steroid hormones: e.g., sex hormones, glucocorticoids, mineralocorticoids
- Amino acid derivatives, e.g., Thyroxine (T_4), triiodothyronine (T_3), epinephrine, norepinephrine etc.

B) Based on the mechanism of action:

Hormones can also be classified into two broad groups based on the location of receptors to which they bind and the signals used to mediate their action.

Group 1 hormones:

These hormones bind to intracellular receptors to form receptor-hormone complexes, through which their biochemical functions are mediated. These hormones act through the intracellular receptors located either in the cytosol or the nucleus. The hormone receptor complex binds to specific regions on the DNA (hormone responsive element) and causes increased expression of specific genes. The ultimate outcome is the production of specific proteins in response to hormonal action. Steroid hormones and thyroid hormone act by this mechanism.

Group 2 hormones:

These hormones bind to cell surface (plasma membrane) receptors and stimulate the release of second messengers (certain molecules). These messengers perform the biochemical functions. These hormones are hydrophilic in nature and usually transported in the free form and possess short half-lives. These hormones can be further divided into three categories based on the chemical nature of the second messengers. The hormones are ACTH, FSH, LH, PTH, glucagon and calcitonin. These stimulate release of second messengers-cAMP. The hormones TRH, gastrin etc. that stimulate release of phosphatidyl inositol/calcium as second messenger. The hormones such as growth hormones, insulin, oxytocin, prolactin etc. The secondary messengers released by these hormones is Protein kinase.[4]

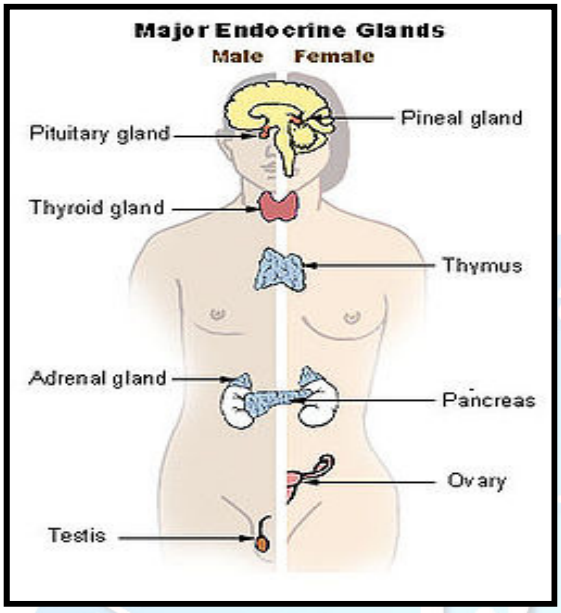


Fig. 1:- Endocrine glands

2. Hormonal Receptors and Mechanism of action of Hormones [5]

A receptor is a protein molecule, embedded in either the plasma membrane or cytoplasm of a cell, to which a mobile signaling (or "signal") molecule may attach. A molecule which binds to a receptor is called a "ligand," and may be a peptide (such as a neurotransmitter), a hormone, a pharmaceutical drug, or a toxin, and when such binding occurs, the receptor goes into a conformational change which ordinarily initiates a cellular response. However, some ligands merely block receptors without inducing any response (e.g. antagonists). Ligand-induced changes in receptors result in physiological changes which constitute the biological activity of the ligands.

Despite the molecular diversity of hormones, all hormone receptors can be categorized into one of two types, based on their location within the cell.

Table.1:- Types of Hormone Receptor

Location of Receptor	Classes of Hormones	Principle Mechanism of Action
Cell surface receptors (plasma membrane)	Proteins and peptides hormones	Generation of second messengers which alter the activity of other molecules - usually enzymes - within the cell
Intracellular receptors (cytoplasm and/or nucleus)	Steroids and thyroid hormones	Alter transcriptional activity of responsive genes

2.1. Hormones with Cell Surface Receptors.[6]

Protein and peptide hormones, catecholamines like epinephrine, and eicosanoids such as prostaglandins find their receptors decorating the plasma membrane of target cells. Binding of hormone to receptor initiates a series of events which leads to generation of so-called second messengers within the cell (the hormone is the first messenger). The second messengers then trigger a series of molecular interactions that alter the physiologic state of the cell. Another term used to describe this entire process is signal transduction.

2.1.1 Second Messenger Systems[7]

There are three basic types of secondary messenger molecules:

Hydrophobic molecules: water-insoluble molecules, like diacylglycerol, and phosphatidylinositols, which are membrane-associated and diffuse from the plasma membrane into the intermembrane space where they can reach and regulate membrane-associated effector proteins

- Hydrophilic molecules: water-soluble molecules, like cAMP, cGMP, IP_3, and Ca^{2+}, that are located within the cytosol.
- Gases: nitric oxide (NO) and carbon monoxide (CO), which can diffuse both through cytosol and across cellular membranes.

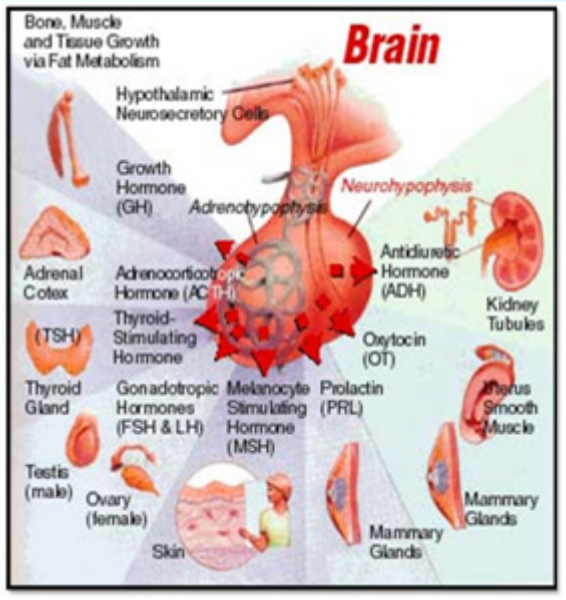


Fig. 2 .Physiology of endocrine system:

These intracellular messengers have some properties in common: They can be synthesized/released and broken down again in specific reactions by enzymes or ion channels. Some (like Ca^{2+}) can be stored in special organelles and quickly released when needed.

Their production/release and destruction can be localized,

enabling the cell to limit space and time of signal activity. Currently, four second messenger systems are recognized for hormones in cells, as summarized in the table below. Note that not only do multiple hormones utilize the same second messenger system, but a single hormone can utilize more than one system. Understanding how cells integrate signals from several hormones into a coherent biological response remains a challenge.

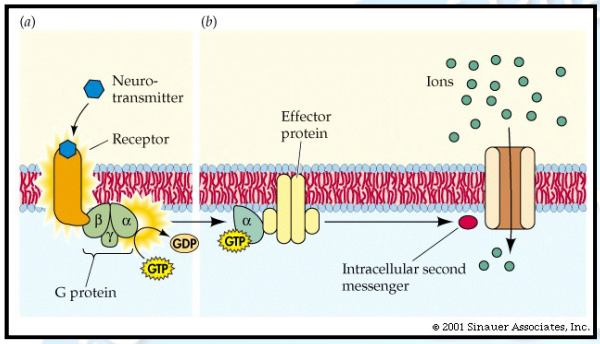


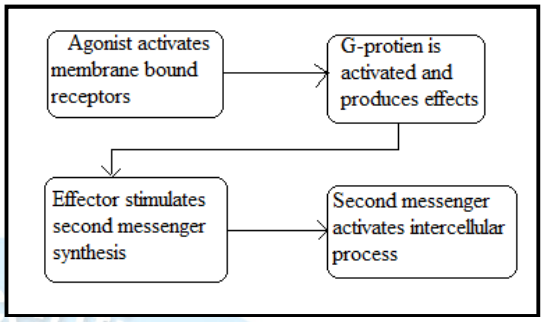
Fig. 3 Hormones with Cell Surface Receptors.

Table.2:- Messenger systems for hormones in cells

Second Messenger	Examples of Hormones Which Utilize This System
Cyclic AMP	glucagon, luteinizing hormone, follicle stimulating hormone, thyroid-stimulating hormone, calcitonin, parathyroid hormone, antidiuretic hormone
Protein kinase activity	Insulin, growth hormone, prolactin, oxytocin, several growth factors, somatostatin.
Calcium and/or phosphatidyl inositol	angiotensin II, antidiuretic hormone, gonadotropin-releasing hormone, thyroid-releasing hormone.
Cyclic GMP	Atrial naturetic hormone.

2.1.2 Common mechanisms of secondary messenger systems8

General Schematic of Second Messenger Mechanism



Hormones with Intracellular Receptors

Receptors for steroid and thyroid hormones are located inside target cells, in the cytoplasm or nucleus, and function as ligand-dependent transcription factors. The hormone-receptor complex binds to promoter regions of responsive genes and stimulates or sometimes inhibits transcription from those genes. Thus, the mechanism of action of steroid hormones is to modulate gene expression in target cells. By selectively affecting transcription from a battery of genes, the concentration of those respective proteins are altered, which clearly can change the phenotype of the cell.

Nuclear receptors are a class of proteins found within the interior of cells that are responsible for sensing the presence of steroid and thyroid hormones and certain other molecules. In response, these receptors work in concert with other proteins to regulate the expression of specific genes thereby controlling the development, homeostasis, and metabolism of the organism.

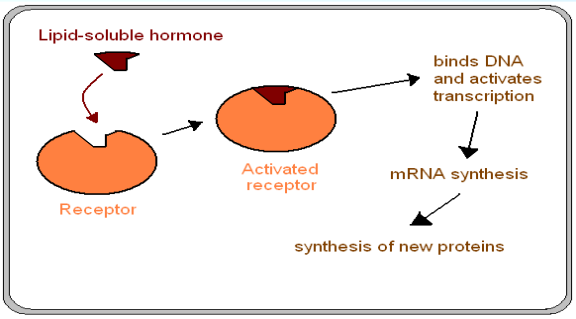


Fig. 4.Mechanism of Intracellular receptors

Nuclear receptors have the ability to directly bind to DNA and regulate the expression of adjacent genes, hence these receptors are classified as transcription factors. The regulation of gene expression by nuclear receptors only happens when a ligand a molecule which affects the receptor's behavior is present. More specifically, ligand binding to a nuclear receptor results in a conformational change in the receptor which in turn activates the receptor resulting in up-regulation of gene expression.

A unique property of nuclear receptors which differentiate them from other classes of receptors is their ability to

directly interact with and control the expression of genomic DNA. Consequently nuclear receptors play key roles in both embryonic development and adult homeostasis. As discussed in more detail below, nuclear receptors may be classified either according to mechanism or homology.

2.2. Structure of Intracellular Receptors

Steroid and thyroid hormone receptors are members of a large group ("superfamily") of transcription factors. In some cases, multiple forms of a given receptor are expressed in cells, adding to the complexity of the response. All of these receptors are composed of a single polypeptide chain that has, in the simplist analysis, three distinct domains:

The amino-terminus: In most cases, this region is involved in activating or stimulating transcription by interacting with other components of the transcriptional machinery. The sequence is highly variable among different receptors.

DNA binding domain: Amino acids in this region are responsible for binding of the receptor to specific sequences of DNA.

The car boxy-terminus or ligand-binding domain: This is the region that binds hormone.

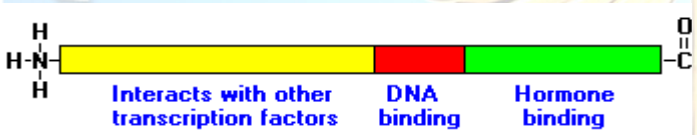


Fig .5. Structure of Intracellular Receptors

In addition to these three core domains, two other important regions of the receptor protein are a nuclear localization sequence, which targets the the protein to nucleus, and a dimerization domain, which is responsible for latching two receptors together in a form capable of binding DNA.

2.3Types of Nuclear receptors[9]

Nuclear receptors (NRs) may be classified into two broad classes according to their mechanism of action and subcellular distribution in the absence of ligand. Small lipophilic substances such as natural hormones diffuse past the cell membrane and bind to nuclear receptors located in the cytosol (type I NR) or nucleus (type II NR) of the cell. This causes a change in the conformation of the receptor which depending on the mechanistic class (type I or II), triggers a number of down stream events that eventually results in up or down regulation of gene expression.

Accordingly, nuclear receptors may be subdivided into the following four mechanistic classes;

Type I:-

Ligand binding to type I nuclear receptors in the cytosol (includes members of the NR subfamily 3) results in the dissociation of heat shock proteins, homo-dimerization, translocation (*i.e.*, active transport) from the cytoplasm into the cell nucleus, and binding to specific sequences of DNA known as hormone response elements (HRE's). Type I nuclear receptors bind to HREs consisting of two half sites separated by a variable length of DNA and the second half site has a sequence inverted from the first (inverted repeat). The nuclear receptor/DNA complex then recruits other proteins which transcribe DNA downstream from the HRE into messenger RNA and eventually protein which causes a change in cell function.

Type II:-

Type II receptors (principally NR subfamily 1) in contrast are retained in the nucleus regardless of the ligand binding status and in addition bind as hetero-dimers (usually with RXR) to DNA. In the absence of ligand, type II nuclear receptors are often complexes with corepressor proteins. Ligand binding to the nuclear receptor causes dissociation of corepressor and recruitment of coactivator proteins. Additional proteins including RNA polymerase are then recruited to the NR/DNA complex which transcribes DNA into messenger RNA.

Type III:-

Type III nuclear receptors (principally NR subfamily 2) are similar to type I receptors in that both classes bind to DNA as homodimers. However, type III nuclear receptors, in contrast to type I, bind to direct repeat instead of inverted repeat HREs.

Type IV:-

Type IV nuclear receptors bind either as monomers or dimers, but only a single DNA binding domain of the receptor binds to a single half site HRE. Examples of type IV receptors are found in most of the NR subfamilies.[10]

2.2.4. Mechanism of action Nuclear receptor (Type II):-11

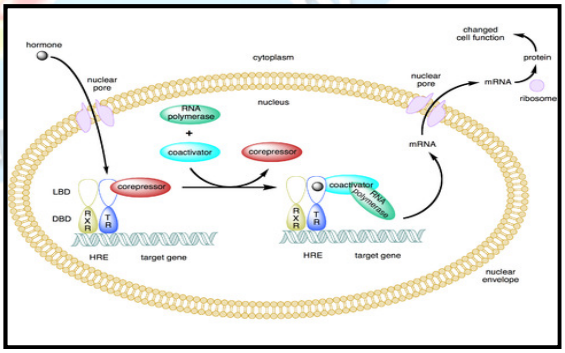


Fig. 6.Mechanism of action of nuclear receptor (Type II)

This figure depicts the mechanism of a class II nuclear receptor (NR) which, regardless of ligand binding status is located in the nucleus bound to DNA. For the purpose of illustration, the nuclear receptor shown here is the thyroid hormone receptor (TR) heterodimerized to the RXR. In the absence of ligand, the TR is bound to corepressor protein. Ligand binding to TR causes a dissociation of corepressor and recruitment of coactivator protein which in turn recruit additional proteins such as RNA polymerase that are responsible for transcription of downstream DNA into RNA and eventually protein which results in a change in cell function.

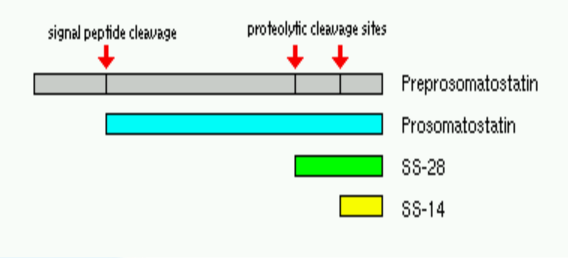
3. Somatostatin [12, 13]

Somatostatin is a neuropeptide that is widely distributed throughout the CNS and peripheral tissues. It potently inhibits basal and stimulated hormone secretion from endocrine and exocrine cells and functions as a neurotransmitter in the CNS, with effects on locomotors activity and cognitive functions. Somatostatin was first discovered in hypothalamic extracts and identified as a hormone that inhibited secretion of growth hormone. Subsequently, somatostatin was found to be secreted by a broad range of tissues, including pancreas, intestinal tract and regions of the central nervous system outside the hypothalamus.

Since its discovery three decades ago as an inhibitor of growth hormone (GH) release from the pituitary gland, somatostatin has attracted much attention because of its functional role in the regulation of a wide variety of physiological functions in the brain, pituitary, pancreas, gastrointestinal tract, adrenal glands, thyroid, kidney and immune system.2 Its actions include the inhibition of endocrine secretion (e.g. GH, thyroid-stimulating hormone, thyrotrophin-releasing hormone and corticotrophin releasing hormone, gastrin, insulin, glucagon, cholecystokinin, vasoactive intestinal peptide and secretin) and exocrine secretion (gastric and pancreatic secretions and intestinal fluid), as well as the inhibition of intestinal motility, absorption of nutrients and ions and vascular contractility. In addition to its modulatory role in neurotransmission and cognitive function, the peptide controls the proliferation of normal and tumour cells.

3.1 Structure and Synthesis of somatostatin [14]

Two forms of somatostatin are synthesized. They are referred to as SS-14 and SS-28, reflecting their amino acid chain length. Both forms of somatostatin are generated by proteolytic cleavage of prosomatostatin, which itself is derived from preprosomatostatin. Two cysteine residules in SS-14 allow the peptide to form an internal disulfide bond.



The relative amounts of SS-14 versus SS-28 secreted depend upon the tissue. For example, SS-14 is the predominant form produced in the nervous system and apparently the sole form secreted from pancreas, whereas the intestine secretes mostly SS-28. In addition to tissue-specific differences in secretion of SS-14 and SS-28, the two forms of this hormone can have different biological potencies. SS-28 is roughly ten-fold more potent in inhibition of growth hormone secretion, but less potent that SS-14 in inhibiting glucagon release.

3.2 Receptors and Mechanism of Action: [15]

The biological effects of somatostatin are mediated through high-affinity plasma membrane receptors, which are widely distributed throughout many tissues ranging from the central nervous system to the pancreas and gut, as well as the pituitary, kidney, thyroid, lung and immune cells. Five stomatostatin receptors have been identified and characterized, all of which are members of the G protein-coupled receptor superfamily. Each of the receptors activates distinct signalling mechanisms within cells, although all inhibit adenylyl cyclase. Radio ligand binding studies have shown that SST-14 and SST-28 interact with SSTR1–4 with similar affinities, whereas SSTR5 preferentially binds SST-28.

The somatostatin receptors comprise a distinct subgroup of seven transmembrane-segment receptors and are most closely related to the opioid receptor family. There is approximately 30% identity between the sequences of somatostatin and opioid receptors. The somatostatin receptors range in size from 346 to 428 amino acids. There is 45-61% identity between the subtypes and 100 residues are invariant among the somatostatin receptor sequences. The sequences of the seven alpha-helical trdnsmembrane regions are most similar and the NH_2- and COOH-termini are the most divergent both in terms of length and sequence.

Table 3. Cloned somatostatin receptor subtypes

Receptor	Size (Amino Acids)	Selective ligands
SSTR 1	391	None
SSTR2	369	NC8-12, MK 678
SSTR3	418	BIM23056
SSTR4	388	None
SSTRS	364	BIM23052. L362,855

The somatostatin receptors are believed to be glycoproteins. There are one or more consensus sequences for Asn *(N)*-linked glycosylation in the extracellular NH_2-terminal domain of each somatostatin receptor subtype, consistent with a role for oligosaccharide addition in somatostatin receptor function. Recent studies suggest that the carbohydrate component of the somatostatin receptors may be involved in promoting high affinity ligand binding.

Tissue distribution:[16]

The tissue distribution of transcripts encoding the five cloned somatostatin receptor subtypes has been examined using several procedures which differ in sensitivity, including RNA (northern) blotting, RNAase protection, and reverse transcriptase-polymerase chain reaction amplification of cellular RNA. RNA blotting studies indicate that the mRNAs encoding the different somatostatin receptor subtypes are of different sizes and much larger than required to encode an ~400 amino acid protein. They also show that human and rat SSTR2 and rat SSTR4 are encoded by multiple mRNAs of different sizes. The molecular basis for the multiple transcripts is uncertain but could be due to differential polyadenylation generating mRNAs with 3′-untranslated regions of different sizes, multiple transcriptional start sites, or processing of the mRNA at cryptic splice sites as described for mouse SSTR2 mRNA. Additional studies are required to distinguish among these alternatives.

The mRNAs for somatostatin receptor subtypes are widely expressed at different levels in human and rodent tissues and have distinct but overlapping patterns of expression. All subtypes are expressed in the CNS. SSTRl-4 mRNA can be readily detected in adult rat brain by RNA blotting. However, the levels of SSTRS mRNA are much lower and cannot be detected in rat brain by RNA blotting but can be observed using a more sensitive RNAase protection assay.

Table 4. Tissue distribution of Somatostatin receptor mRNAs

Sub types	Species	Tissue
SSTR 1	Human, Rat	small intestine. stomach, lung, brain
SSTR2	Human, Rat	Brain, kidney brain, pituitary,adrenal
SSTR3	Human, Rat	brain brain, pancreatic islets
SSTR4	Human, Rat	brain brain
SSTRS	Human, Rat	Pituitary Pituitary

The pattern of expression of somatostatin receptor mRNA expression in mouse (SSTRl-3) and rat (SSTRl-4) has been examined by in situ hybridization histochemistry. These studies have shown expression of SSTRl-4 mRNA throughout the neocortex, the hippocampal formation and amygdale consistent with a role of somatostatin in regulation of complex integrative activities such as locomotor activity, learning and memory.

SSTR2 and SSTR4 mRNAs are specifically expressed at high levels in the habenula. SSTR2 mRNA is expressed in the medial habenula and SSTR4 mRNA in the lateral portion of this important relay nucleus between the basal ganglia and mesolimbic structures to the serotonin-containing cell bodies of the raphe nuclei.

All five SSTR mRNAs are expressed in the hypothalamus suggesting that these receptors may be involved in the regulation of autonomic and neuroendocrine function. Since somatostatin has been shown to feedback regulate growth hormone releasing factor (GRF) neurons,23 it is possible that SSTR2 may be involved in the control of GRF neuronal activity by somatostatin.

Ligand binding studies have shown that there are few somatostatin receptors in the cerebellum. Somatostatin receptor mRNA has also been identified in peripheral tissues. Several tissues such as pituitary and spleen express high levels of mRNA for the five receptor subtypes, with rank orders of expression of SSTR2 > SSTRl = SSTR3 > SSTR5> SSTR4 for pituitary, and SSTR3 > SSTRl = SSTR4 = SSTR5 > SSTR2 for spleen. Adrenal glands express high levels of SSTR2 mRNA and the heart expresses detectable SSTR5 mRNA. Low levels of mRNA can be identified in many other tissues. Somatostatin receptor mRNA has also been identified in tumours.

3.3 Role of Somatostatin in various receptors[17,18]:

Somatostatin receptors (sst) and somatostatin (SS) are widely expressed in the various systems in the human and rodent organisms and are "responsible" for maintaining homeostasis, which is essential for survival. Because of their broad expression pattern sst and SS interactions may play regulatory roles in both physiology and pathophysiology in mammalian organisms. SS analogue treatment strategies as well as the use of SS analogues for diagnostic purposes have been established in diseases of different origins.

In mammals, proteolytic processing of a 116-amino acid prepro-SS results in the formation of two biologically active forms of SS, consisting of 14 and 28 amino acids, respectively. The amino acid residues Phe7, Trp8, Lys9 and Thr10 are essential for binding of both SS isoforms to their five known receptors, sst1–5 , which are G-protein coupled seven transmembrane receptors,having an N-terminal extracellular domain and C-terminal intracellular domain. Via binding to its receptors SS exerts its multiple effects, which are described extensively in the papers of the present journal. SS is widely expressed throughout the human body, like for instance in the central nervous system, gastro-intestinal tract and endocrine glands. In these tissues/systems SS exerts a mainly inhibitory role on secretion processes. In addition, SS was also shown to have antiproliferative effects on different cell types in vitro.

4 Central actions in the SS and sst network:

4.1 Sleep regulation: [19, 20]

Most of the actions of SS have been designated to the regulation of behavior, sleep and memory mechanisms localized in the brain region. It seem to depress neuronal activity in the hippocampus, reduce development of seizures and can deteriorate memory consolidation. The administration of SS results in sleep periods dominated by REM sleep, without significantly affecting the other phases of sleep. During sleep deprivation also up regulation of SS has been demonstrated in the brain. This suggests that SS have sleep regulatory functions and probably interplay in the regulation of sleep. Previous studies demonstrated that acetylcholine (ACh) is present at low concentration in the cortex during slow-wave sleep, and higher concentrations of ACh are associated with wakefulness and REMsleep. Therefore, the question was addressed whether SS produces its sleep promoting effects by modulating ACh activity. SS is known to enhance the effects of ACh.

4.2 Epilepsy: [21]

Epilepsy is characterized by abnormal hyperexcitation, which can include several different brain regions. Temporal lobe epilepsy (TLE) involves the hippocampus. In tissues removed from patients with TLE a selective loss of SS containing neurons was found in the hilus of the dentate gyrus. Comparable results were found in animal models for epilepsy in which SS containing neuronal loss can extend beyond the hilus to the rest of the hippocampus. Recent studies have investigated the pathways involved in SS neuron loss in epilepsy, and it seems that the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway may be involved. The function of these SS neurons and the consequences of their loss are unknown. However, the majority of SS interneurons make inhibitory synapses onto primary hippocampal neurons, suggesting their involvement in inhibitory processes. The loss of SS neurons in early stages of epilepsy may contribute to subsequent abnormal hippocampal hyperexcitability Intracerebroventricular and intrahippocampal injections of SS and SS analogues have been shown to modulate seizure activity in animal models. Early studies suggested that SS had a stimulatory effect on seizures, however, more recent studies, in which SS was directly injected into the hippocampus, have demonstrated inhibitory effects on electrical seizures recorded in vivo These findings in animal models both in vitro and in vivo show an important role for SS in regulating seizure activities. The exact mechanisms remain to be determined in future studies in transgenic and knock-out mice which allows for temporally and regionally controlled expression and deletion. The potential clinical significance of SS or its analogues with respect to therapeutical options in epilepsy therefore seems to be still far ahead.

4.3 Alzheimer's disease[22]:

AD is the most common type of human dementia which is characterized clinically by a gradual but progressive decline in memory and other cognitive domains and the frequent occurrence of noncognitive behavioral symptoms. At present, available medications appear to be able to produce moderate symptomatic benefits but not to stop disease progression. Therefore, ca. 100 proprietary pharmacological products are currently being developed for an AD treatment. Neuropath logically, the cardinal features of AD in brain include neuritic plaques, neurofibrillary tangles, and the loss of synapses and neurons. A prominent decrease in somatostatin also represents a pathological characteristic of AD, although this defect is not due to a reduction in the rate of proteolytic processing of peptide precursors. A somatostatin deficit occurs in the cerebral cortex and cerebrospinal fluid of AD patients. In particular, in frontal cortex of AD brain, somatostatin-positive neurons decrease (N70%), and glial fibrillary acidic protein-positive astrocytes significantly increase (N130%) in comparison to control brain. In addition, AD-related cytoskeletal changes of interstitial cells (which are isolated neurons located in the infracortical white matter)

is accompanied by loss of somatostatin. Also, a significant decrease in both the number of somatostatin-expressing neurons in the mouse CA1 hippocampal region and in the somatostatin expression level within these neurons seems to be involved in AD pathogenesis. When specific somatostatin receptor subtype has been studied, sst2 and sst4 are the predominant subtypes in frontal cortex of AD brain, followed by sst1, sst3 and sst5. In particular, AD cortex shows a marked reduction (in comparison to control cortex) in neuronal expression of sst4 and sst5 and a modest decrease in sst2-like immunoreactivity without any changes in sst1 immunoreactive neurons. In contrast, sst3 is the only receptor subtype that increases in AD cortex. In addition, sst1-, sst3-, and sst4-like immunoreactivities are strongly expressed in glial cells of the AD cortex, but not sst2 and sst5. Recently, the somatostatin system has been indicated as a potential pharmacological strategy for the prevention of AD. In this respect, pharmacological studies have demonstrated that octreotide infusion alone improves memory for patients with AD. In addition, the activation of somatostatin neurotransmission with FK960 (a somatostatin-releasing agent) or similar drugs has considerable potential in the treatment of cognitive impairment of rhesus monkeys which have developed AD.

5 Neuroendocrine disorders and Somatostatin[23]:

SS was initially identified as a growth hormone release inhibiting factor from the ovine hypothalamus. SS in animals and human, however, was found to exert broader inhibitory effects on hormone secretion, like insulin and glucagon. These inhibitory effects have formed the basis for the application of SS analogues in treatment of endocrine tumors.

5.1 Acromegaly:

Acromegaly is a disorder, characterized by hyper secretion of growth hormone (GH), mainly by pituitary adenomas, leading to elevated circulating GH and insulin-like growth factor I (IGF-I) levels. Over the years treatment strategies consisted of surgery, irradiation and medical treatment in order to induce tumour shrinkage and normalization of GH and IGF-I levels. Therapy aims for reduction of the risk of longterm complications, like development of malignant neoplasms, cardio- and cerebrovascular disease, respiratory and metabolic dysfunction. In GH-secreting pituitary adenomas sst2 and sst5 are the predominantly expressed sst. The introduction of the long-acting SS analogues octreotide and lanreotide in treatment of acromegaly patients, which were shown to decrease GH levels and clinical signs and symptoms, has turned these peptides into the worldwide first medical treatment options for acromegaly. Recent studies have addressed in more detail the involvement of the different sst subtypes in regulating responses to SS analogues.

5.2 Cushing's disease[24]

Cushing's disease is characterized by hyper secretion of adrenocorticotropin hormone (ACTH) by the pituitary gland, resulting in overproduction of cortisol by hyperplastic adrenocortical glands. In Cushing's disease transsphenoidal surgery is the treatment of choice, results reporting success rates between 50 and almost 90%. If surgery fails, radiotherapy may be used. However, none of the treatment strategies ensures full and permanent cure, as the rate of recurrence of disease varies between 5 and 24%. The expression of sst in ACTH-secreting puitary adenomas has led to studies investigating the potential significance of SS analogues in treatment of Cushing's disease. Initial studies in small numbers of patients with the first clinically available SS analogue octreotide showed that octreotide had no significant effects in reducing ACTH levels. Previous studies have demonstrated that glucocorticoids can down regulate sst receptor expression. In an hypercortisolemic state, as in Cushing's disease, sst receptors may be down regulated on pituitary tumor cells, which may explain why SS analogues lack an inhibitory effect on ACTH secretion in Cushing's disease. However, recent progress in multiligand SS analogue development, i.e. SOM230, has again raised interest in potential benefits of these new compounds in Cushing's disease.

5.3 TSH-secreting pituitary adenomas[25]

TSH-secreting pituitary adenoma is a relatively rare disorder and surgery is the most important treatment approach, normalizing thyroid hormone levels in approximately 44% of patients. In patients treated with octreotide, 80% showed normalization of TSH levels, while significant tumors shrinkage was observed in 50%. In a very recent study it was demonstrated that sst2 is the sst sybtype predominantly expressed in a series of TSH-secreting adenomas, and the patient with highest expression of sst2 showed marked shrinkage of the tumour on octreotide treatment. These data suggest that sst2 is involved in control of TSH secretion and SS analogues form a treatment modality in these tumours.

6. SS in the human immune system [26, 27]:

The expression of SS, CST and sst in the human immune system has been investigated in detail recently. Scientist found low-affinity binding sites on resting monocytes and lymphocytes. Using fluorescent SS, sst were identified on mitogen-activated human peripheral lymphocytes. Subsequent studies have characterized the sst subtype expression in cells and tissues of the human immune system in more detail.

The wide expression of sst subtypes in the human im-

mune system suggests a potential functional significance of SS and its receptors in immune cell function. Expression of SS itself has been investigated in cells of the human immune system, however it was demonstrated that SS expression was restricted to the human thymus, and in the human thymus, only in the thymic epithelial cells and not in the lymphoid component. Human monocytes, macrophages, dendritic cells, peripheral blood mononuclear cells, bone marrow and spleen did not show SS expression. Therefore it was suggested that SS may act via the sst expressed on immune cells via the innervating neurons, as lymphoid organs are highly innervated. The functional significance of SS in the human immune system remains largely unknown, although different potential effects have been described in previous studies.

Cell proliferation[28,29,30]:
It is known that sst1, sst2, sst4 and sst5 are able to arrest cell growth and thus may contribute to an antiproliferative effect of SS. On the other hand, sst3 is involved in apoptosis. In recent years both inhibitory and stimulatory effects of SS or its analogues on cell proliferation have been described. Until now it remains unclear which is the functional significance of SS with respect to controlling cell proliferation in human immune cells in vivo.

Secretion processes:
SS is mainly known for its inhibitory actions on secretion processes, like for instance in the neuroendocrine system. In the human immune system SS was found to have a predominant inhibitory effect on secretion of cytokines and immunoglobulins, albeit mainly in studies performed in vitro.

Migratory effects:
SS may be a mediator of the regulation of migration of immune cells towards sites of inflammation. SS controls adhesion of T-lymphocytes to fibronectin, an important glycoprotein of extracellular matrix and, more recently, it has been demonstrated that SS may act as a chemo- attractant to human primitive haematopoietic cells. Therefore, SS may play a role in inflammatory processes by directing immune cells towards the sites of inflammation, or SS may play a role in regulation of development of immature immune cells. SS itself is not expressed in cells of the human immune system. Thus, it was hypothesized that SS reaches its receptors in these cells via innervating nerve endings.

7. Somatostatin analogue [31, 32]
Somatostatin analogues may inhibit the growth of tumors by triggering on the signaling cascades that negatively control cell growth. These include the ''direct mechanisms''that are sequelae of the binding of somatostatin analogues to sst on neoplastic cells .The ''indirect mechanisms''are related to the effects of the binding of somatostatin analogues to sst present on normal cells of the host.

Direct mechanisms of somatostatin analogues
A large variety of primary tumors and their metastasis express a high density of sst Analysis of sst mRNAs demonstrates that human tumors from neuroendocrine and gastroenteropancreatic origin, gliomas, meningioma's, prostrate, lung, and breast tumors express multiple somatostatin subtypes; sst2 being the most frequently expressed. The role of sst2 in the negative control of cell proliferation is further strengthened by the presence of this subtype in human breast cancer cells, carcinoid tumors, small cell lung carcinoma cells, and pancreatic cancer cells,which therapeutically respond in vitro and in vivo to somatostatin analogues. The majority of these tumors also express sst5 and, to a lesser extent, sst1, sst3, and sst4.
The antiproliferative action of somatostatin analogues can lead to cytostasis or apoptosis depending on the receptor subtype expressed on target cells. Sst2 primarily mediates the antiproliferative effect of somatostatin analogues in vitro, by activation of the phosphotyrosine phosphatase SHP-1 . The inhibition of tyrosine kinase by somatostatin analogues like RC-160 and TT2-32 has been also implicated in the negative control of cell proliferation Sst1,2A, 4, and 5 induce G1 arrest by down-regulating the phosphorylation of retinoblastoma. Sst1 can also cause cell cycle arrest by activation of the Ras/MAPK pathway and subsequent induction of cdk inhibitor p21Waf-1/Cip-1. Sst5 inhibits cell growth by down-regulating the MAPK pathway via a guanylyl cyclase sensitive mechanism. The apoptosis of cancer cells (in response to octreotide therapy) seems to be mediated uniquely via the SSTR3 subtype, on target cells, via a mechanism involving intracellular acidification, activation of endonuclease, and induction of p53 and Bax .Whereas apoptosis is triggered at low agonist concentration (z0.1 nM), cytostasis is induced at much higher (>50 nM) agonist concentrations. Recently, sst2 has also been found to mediate apoptosis via a p53 independent pathway. In addition TT2-32 can also cause apoptosis by sustained activation of JNK and p38 kinase cascade with concomitant blockage of the extracellular-regulated kinase 2 (ERK2) signaling pathway Besides, the antiproliferative effect of somatostatin dueto cytostasis and/or apoptosis, somatostatin has been shown to exert its antineoplastic actions by inhibiting the synthesis of mitogenic hormones, growth factors, and cytokines, mediated by inhibition of cAMP and calcium production .

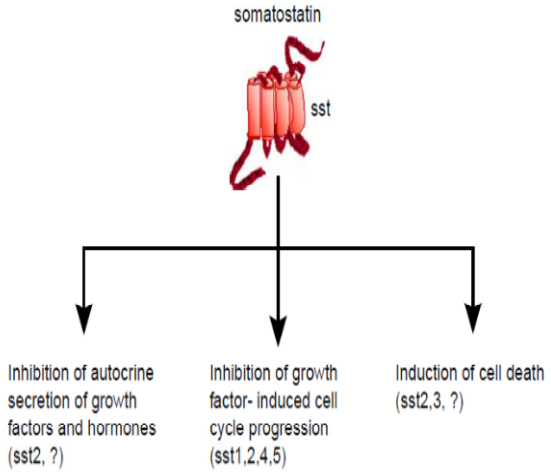


Fig 7 Mechanisms of direct antiproliferative effects of somatostatin[33]

Additionally, somatostatin can interfere with the exocytotic machinery by down-regulating the protein phosphatase calcineurin .

Indirect mechanisms of somatostatin analogues[34]

The antineoplastic action of a somatostatin analogue is classified as indirect if it is a consequence of binding of the analogue to sst present on normal cells of the host . This effect may be mediated by the following mechanisms:

Inhibition of growth factors like epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), insulin-like growth factors I and II (IGF-I and IGF-II, respectively), and insulin-like growth factor binding protein.The importance of growth factors and gastrointestinal hormones in the etiology growth and pathogenesis of several carcinomas has long been recognized. Growth factors like EGF, IGFI,bFGF, and platelet derived growth factor (PDGF) appear to be implicated in the proliferation of many types of cancer cells such as pancreatic, prostate, mammary, colorectal carcinoma, etc. The neuropeptide somatostatin is known to be a potent inhibitor of exocrine and endocrine secretion of these growth factors. octreotide is a potent inhibitor of Swarm's chondrosarcoma, an experimental neoplasm,which lacks the sst .

These chondrosarcoma cells have abundant IGF-I recetors and it waspropose that this growth inhibition is mediated indirectly through octreotide-induced suppression of pituitary GH secretion, which in turn leads to reduction in GH dependent hepatic IGF expression.

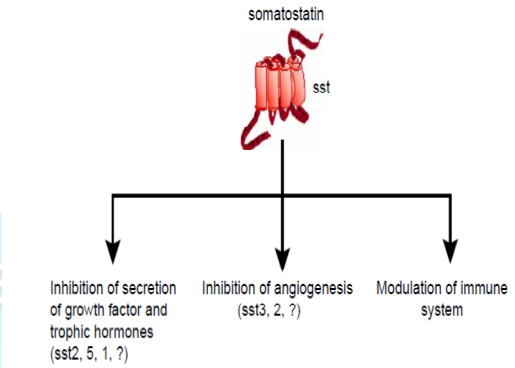


Fig 8 Mechanisms of indirect antiproliferative effects of somatostatin

The GH-IGF-I axis has an important influence on the biological behavior of many neoplasms. Many types of neoplastic cells display IGF-I receptors and respond mitogenically to insulin-like growth factors present in their microenvironment. The suppressive effect of somatostatin analogues on serum IGF-I levels may be related to the direct inhibition of IGF-I gene expression as well as to the suppression of GH, which in turn inhibits IGF-I.

7.1 Somatostatin analogues in retinopathy[35]

Somatostatin agonists can inhibit retinal endothelial cell proliferation and angiogenesis both by direct and indirect mechanisms in proliferative retinopathy. The somatostatin analogue octreotide has been shown to exert a direct inhibitory effect on the proliferation and migration of human retinal endothelial cells induced by IGF-I and bFGF. They found that somatostatin analogues can induce cell cycle arrest via sst2 as well as endothelial apoptosis via sst3-coupled pathways. Several animal models have been also been used to test the efficacy of somatostatin agonists in diabetic retinopathy. Twice-daily systemic octreotide injection in rat model caused about a 60% decrease in serum GH levels. However, there was no signification ablation of retinal neovascularization in response to octreotide therapy. In contrast,found that somatostatin agonists octreotide and Woc4D significantly decreased oxygen-induced retinal neovascularization in neonatal mouse models, as measured by the reduction in the number of neovascular tufts and extraretinal neovascularization in mice treated with either analogue, relative to control animals. The study also found a potent reduction in the levels of GH mRNA in these mice.

Age-related macular degeneration (ARMD) is the leading cause for blindness in elderly people. Although the pathogenesis of the disease is not fully understood, it is known that choroidal neovascularization causes newly formed blood vessels to grow beneath the RPE. The

neovascular form of ARMD is characterized by choroidal angiogenesis, leakage of blood or serum, and detachment of RPE, which finally leads to scarring of the macula.

7.2 Somatostatin analogues in diabetic nephropathy[36]

The human kidney expresses several subtypes of sst mRNA, with a quite specific expression of sst5 in tubular epithelial cells. Sst1 and sst2 are have been found in the tubules and glomeruli of human kidney. In addition, somatostatin regulates important physiological functions of the kidney, including glomerular filtration rate, prostaglandin synthesis, and water, phosphate, and sodium excretion. In short-term experimental diabetes, administration of octreotide was found to inhibit increase in renal hypertrophy, which correlated with blunting of IGF-I levels. Furthermore, octreotide therapy has been shown to suppress urinary protein excretion, inhibit serum and kidney IGF-I levels and attenuate renal enlargement in diabetic animal models and patients . The administration of octreotide was found to significantly ablate increased glomerular filtration rate and kidney size in patients with insulin-dependent diabetes. Although these studies show that somatostatin agonists possess therapeutic promise for diabetic nephropathy, further research is necessary to define the roles of somatostatin and its receptor subtypes in diabetic renal complications. The biochemical pathways underlying somatostatin action in the kidneys needs to be elucidated to design potent and selective somatostatin agonists that are useful for the treatment of this disease.

7.3 Example of Somatostatin analogues

a) Octreotide[37]

These are hormone are used to treat the cancer. This medication is given to control symptoms such as diarrhea or flushing in patient with tumors such as carcinoid, gastrinoma, or vasoactive intestinal peptide-secreting tumors.it is also used to treat acromegaly.

Mechanism of action

Octeretiode is similar to natural chemical called somatostatin .somatostatin is produced in the body by hypothalamus. One of its function is to switch off the secretion of growth harmone by the pituitary gland . Somatostatin also decreses splanchnic blood flow and inhibit the relese of serotonin ,gastrin vasoactive intestinal peptide and pancreatic polypeptide.these action help to control the symptoms of flushing and diarrhea in carcinoid tumors.octeride is very stable and therefore much more long acting than somatostatin.

Pharmacological Effects:

Octreotide inhibits secretion of many hormones, such as gastrin, cholecystokinin, glucagon, growth hormone insulin, secretin, pancreatic polypeptide, TSH, and vasoactive intestinal peptide. It reduces secretion of fluids by the intestine and pancreas. It also causes reduction in gastrointestinal motility and inhibit contraction of the gallbladder. It Inhibits the action of certain hormones from the anterior pituitary, causes vasoconstriction in the blood vessels. It reduces portal vessel pressures in bleeding varies. It has also been shown to produce analgesic effects, most probably acting as a partial agonist at the μ opioid receptor.

Adverse effects

Most Frequent Adverse Effects: Abdominal pain with cramps, bradycardia, cardiac conduction changes, gastrointestinal reactions (including nausea/vomiting and diarrhea or constipation), injection site reactions, nausea, vomiting.

Less Frequent Adverse Effects: Discolored feces, dyspepsia, flatulence.

Rare Adverse Effects: Acute pancreatitis, alopecia, biliary calculi, liver failure, dizziness, edema, fatigue, fever, flushing, generalized weakness, headache, hepatitis, hyperbilirubinemia.

Uses

The Food and Drug Administration (FDA) has approved the usage of a salt form of this peptide octreotide acetate, as an injectable depot formulation for the treatment of acromegaly, the treatment of diarrhea and flushing episodes associated with carcinoid syndrome, and treatment of diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas). Octreotide has also been used off-label for the treatment of severe, refractory diarrhea from other causes. It is used in toxicology for the treatment of prolonged recurrent hypoglycemia after sulfonylurea and possibly meglitinides overdose. Octreotide has also been used with varying degrees of success in infants with Nesidioblastosis to help decrease insulin hyper secretion In patients with suspected esophageal varices, octreotide can be given to help decrease bleeding. Octreotide has been investigated for patients with pain from chronic pancreatitis.

Octreotide may be useful in the treatment of thymic neoplasms. It has been used in the treatment of malignant bowel obstruction. Octreotide may be used in conjunction with midodrine to partially reverse peripheral Vasodilation in the hepato-renal syndrome by increasing systemic vascular resistance, these drugs reduce shunting and improve renal perfusion, prolonging survival until definitive treatment with liver transplant.

b) Lanreotide (INN)[38]

Lanreotide is a medication used in the management of

acromegaly and symptoms caused by neuroendocrine tumors, most notably carcinoid syndrome. It is a long-acting analogue of somatostatin, like octreotide

Mechanism of action

Lanreotide is a synthetic analogue of somatostatin, a naturally occurring inhibitory hormone which blocks the release of several other hormones, including growth hormone, thyroid-stimulating hormone (TSH), insulin and glucagon. Lanreotide binds to the same receptors as somatostatin, although with higher affinity to peripheral receptors, and has similar activity. However, while somatostatin is quickly broken down in the body (within minutes), lanreotide has a much longer half-life, and produces far more prolonged effects

The efficacy of lanreotide has not been extensively studied, and results differ greatly between trials and formulations.

Indication

Lanreotide is used in the treatment of acromegaly, due to both pituitary and non-pituitary growth hormone-secreting tumors, and the management of symptoms caused by neuroendocrine tumors, particularly carcinoid tumors and VIPomas. In the United States and Canada, lanreotide is only indicated for the treatment of acromegaly. In the United Kingdom, it is also indicated in the treatment of thyrotrophic adenoma,[4] a rare tumor of the pituitary gland which secretes TSH.

Interestingly, lanreotide also shows activity against non-endocrine tumors, and, along with other somatostatin analogues, is being studied as a possible general anti-tumor agent.

Side effect

The main side effects of lanreotide treatment are mild to moderate pain at the injection site and gastrointestinal disturbances, such as diarrhea, nausea and vomiting. Isolated cases of gallstone formation have been associated with use of lanreotide, particularly over long periods of time.

Formulation

Lanreotide is available in two formulations: a sustained release formulation (sold under the trade name Somatuline LA), which is injected intramuscularly every ten or fourteen days, and an extended release formulation (UK trade name Somatuline Autogel, or Somatuline Depot in the U.S.), which is administered subcutaneously once a month.

C) VAPREOTIDE[39]

Vapreotide is a synthetic octapeptide somatostatin analog. It was being studied for the treatment of cancer.

Mechanism Of Action: The exact mechanism of action is unknown, although one study has provided in vitro and in vivo evidence for a tachykinin NK1 receptor antagonist effect in the analgesic effects of vapreotide.

PharmacologyVapreotide is a somatostatin analog with a higher metabolic stability than the parent hormone. Vapreotide reduces splanchnic blood flow; inhibits growth hormone release, and inhibits the release of peptides and vasoactive compounds from neuroendocrine tumors.

Toxicity

Safety data are limited, however, headache, fatigue, diarrhea, nausea, vomiting, and abdominal pain have been reported commonly with the use of vapreotide.

D) Pasireotide [40]

A synthetic long-acting cyclic peptide with somatostatin-like activity. Pasireotide activates a broad spectrum of somatostatin receptors, exhibiting a much higher binding affinity for somatostatin receptors 1, 3, and 5 than octreotide in vitro, as well as a comparable binding affinity for somatostatin receptor 2. This agent is more potent than somatostatin in inhibiting the release of human growth hormone (HGH), glucagon, and insulin.

Mechanism of action

Pasireotide suppressed GH levels similar extent or greater extent than octreotide, indicating that it may be effective in patients with octreotide-resistant acromegaly. Furthermore, using stringent criteria, the majority of patients did not demonstrate relevant changes in glucose metabolism by the end of the pasireotide treatment period.

Side effect

The main side effects of Pasireotide treatment are mild to moderate pain at the injection site and gastrointestinal disturbances, such as diarrhea, nausea and vomiting. Isolated cases of gallstone formation have been associated with use of Pasireotide, particularly over long periods of time.

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