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Biochemistry and Physiology of Gastrointestinal Somatostatin

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Somatostatin, a tetradecapeptide initially isolated from the ovine hypothalamus, is widely distributed throughout the gastrointestinal tract where it may act as a hormone, local chemical messenger, or neurotransmitter to elicit many physiological actions. Release of somatostatin from D cells in the gut is regulated by mechanisms that are both dependent on and independent of cAMP. In most cases somatostatin acts to inhibit the function of its target cells. It performs this action in part via pertussis-toxin-sensitive inhibitory guanine nucleotide-binding proteins that regulate adenylate cyclase activity. Other mechanisms may involve sites of action distal to intracellular second messenger systems.

KEY WORDS: somatostatin; gastrointestinal tract.

The story of the discovery and isolation of somatostatin is one in which an unexpected and unexplained observation was pursued with great application to yield novel and far-reaching results. In 1968, while searching for an hypothalamic growth hormone releasing factor, Krulich et al (1) found that fractions obtained on chromatography of sheep or rat hypothalamus had the effect of inhibiting growth hormone release from rat anterior pituitary. Subsequently, investigators in Guillemin's laboratory made a similar observation, and they set out to identify the cause of this phenomenon. In the course of their labors they isolated from 500,000 sheep hypothalami, a peptide we now call somatostatin-14 (S14), and by stepwise Edman degradation they determined its structure (2, 3). They described a 14-amino acid peptide with a cyclic conformation maintained by an intramolecular disulfide bond linking two cysteine residues (Figure 1).

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This peptide inhibited release of growth hormone from somatotrophs. Following this advance, many other inhibitory actions of somatostatin were described. In 1975, Arimura et al (4, 5) described the first radioimmunoassay for somatostatin and, thereafter the widespread distribution of somatostatin both within mammalian tissues and throughout the phylogena became clear. Somatostatin is present in virtually every tissue in the mammalian body, in all classes of vertebrate, in protochordate plants, protozoa, and even prokaryotes. Four interrelated functions have been proposed for somatostatin in man—that of neurohumoral regulator, neurotransmitter, endocrine hormone, and paracrine hormone.

This review will outline current understanding of the biochemistry, tissue distribution, release, and physiological function of gastrointestinal somatostatin and place particular emphasis on recent advances concerning the cellular aspects of release and mechanism of action of somatostatin.

STRUCTURE AND BIOSYNTHESIS

Since its initial purification, somatostatin-14 (S14) has been isolated and its amino acid sequence determined from a variety of species and tissues

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	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
S14															Ala	Gly	Cys	Lys	Asn	Phe	Phe	Trp	Lys	Thr	Phe	Thr	Ser	Cys
S28	Ser	Ala	Asn	Ser	Asn	Pro	Ala	Met	Ala	Pro	Arg	Glu	Arg	Lys	Ala	Gly	Cys	Lys	Asn	Phe	Phe	Trp	Lys	Thr	Phe	Thr	Ser	Cys
Catfish S22							Asp	Asn	Thr	Val	Thr	Ser	Lys	Pro	Leu	Asn	Cys	Met	Asn	Tyr	Phe	Trp	Lys	Ser	Arg	Thr	Ala	Cys
Anglerfish I	Ala	Ala	Ser	Gly	Gly	Pro	Leu	Leu	Ala	Pro	Arg	Glu	Arg	Lys	Ala	Gly	Cys	Lys	Asn	Phe	Phe	Trp	Lys	Thr	Phe	Thr	Ser	Cys
Anglerfish II	Ser	Val	Asp	Ser	Thr	Asn	Asn	Leu	Pro	Pro	Arg	Glu	Arg	Lys	Ala	Gly	Cys	Lys	Asn	Phe	Tyr	Trp	Lys	Gly	Phe	Thr	Ser	Cys

Fig 1. Amino acid sequences of somatostatins (from reference 66).

including porcine hypothalamus (6), anglerfish pancreatic islets (7), guinea pig stomach and pancreas (8), catfish pancreas (9), and frog brain (10). Although when amino acid sequences are deduced from cloned mRNA in some species the possibility of variability in the S14 amino acid sequence has been raised, in fact all S14 identified to date have been identical to that originally described. This represents a remarkable degree of phylogenetic preservation.

In 1978, Pradayrol et al (11) reported the purification and sequencing of a larger somatostatin isolated from porcine intestine. It consisted of 28 amino acids (S28) and contained the S14 moiety at its carboxyl terminus linked to the first 12 amino acids by an Arg-Lys dipeptide (Figure 1). Subsequent studies have shown that S28, in contrast to S14, can have considerable interspecies variation, especially when isolated from fish. S28 exerts many actions when administered *in vivo* and *in vitro*. While these are frequently of a similar nature to those of S14, there are considerable differences between the two moieties in specific actions, potency, and metabolism (see below). The relative importance of S14 and S28 as physiological effectors remains a subject of debate.

By application of recombinant DNA technology, larger precursor forms of somatostatin comprising more than 100 amino acids have been discovered. These have been called preprosomatostatins. cDNAs encoding anglerfish (12), catfish (13), rat (14), and human preprosomatostatin (15) have been isolated and cloned. In each case S28 is found to occupy the carboxyl terminus. The presence of multiple mRNAs encoding somatostatin in anglerfish and catfish pancreata is of particular interest, indicating that in submammalian species there may be expression of different genes for somatostatin within the same organ. The structural genes for human (16) and rat (17, 18) somatostatin have been cloned and are quite similar in overall conformation.

Figure 2 describes some of the possible routes for posttranslational processing of somatostatin precursors to S28 and S14. It is uncertain whether in mammals S28 is formed first and then cleaved to

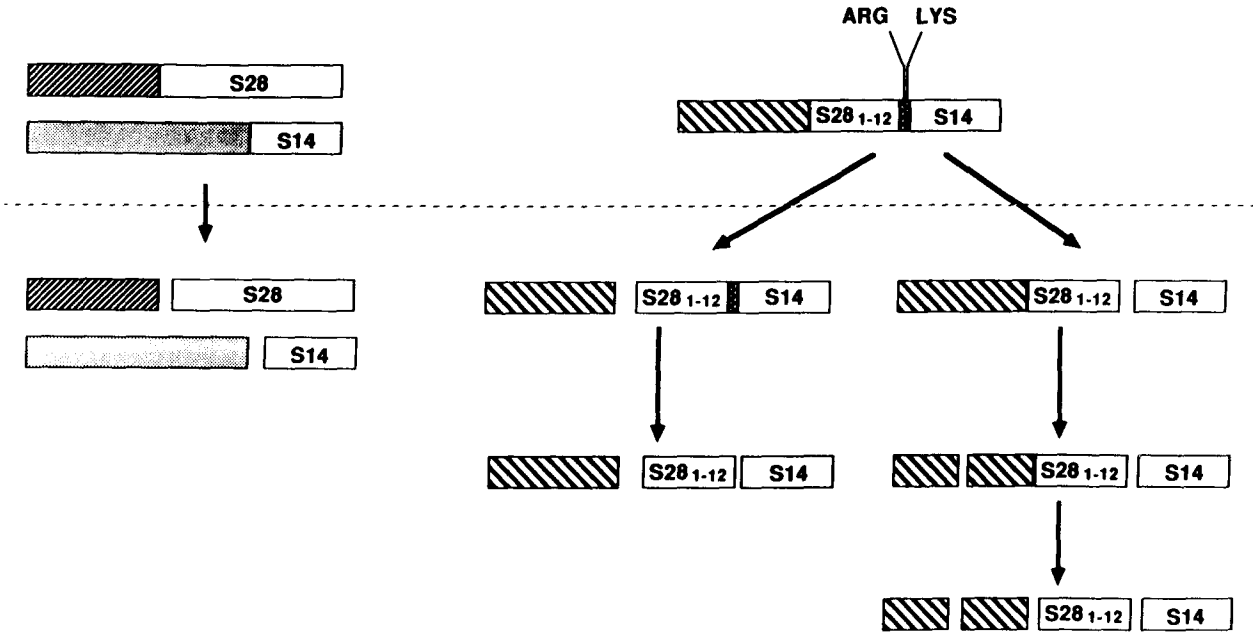

Fig 2. Alternative mechanisms for preprosomatostatin posttranslational processing (from reference 66).

S14 and a remnant peptide (28_{12}) or whether S28 and S14 are each derived directly from larger precursors. Not only is intraspecies variation in post-translational processing likely, but also within the same species, different tissues may process somatostatin precursors differently. This conclusion is strongly supported by the striking differences in distribution of S14 and S28 throughout the mammalian gastrointestinal tract (see below).

TISSUE DISTRIBUTION

As stated above, somatostatin is almost ubiquitous in the mammalian body. The gastrointestinal tract and pancreas contain the greatest amounts of somatostatin. The majority of somatostatin in the human gut is confined to the mucosal layer where it is localized in endocrine cells, termed D cells. The remainder is present in neural cells, in which it forms part of the peptidergic neural system. In the stomach there are important differences between the D cells of the fundus and those of the antrum. Fundic D cells are of a "closed type," with no obvious luminal contacts; antral D cells are of an "open type," with their apical membrane exposed to the gastric lumen (19). As a consequence, it has been suggested that antral D cells respond to luminal stimuli, whereas fundic D cells do not. Both fundic and antral D cells possess long cytoplasmic extensions that appear to abut on effector cells—parietal and chief cells in the fundus, gastrin cells in the antrum (20–22). The presence of these cytoplasmic extensions has been interpreted as evidence for a local or paracrine route of action for somatostatin.

Duodenal D cells are typical flasklike endocrine cells with their apical membranes open to the intestinal lumen (21). In jejunum and ileum, somatostatin is located most commonly in neurons (23, 24). There is little somatostatin in the colon.

S14 is the predominant molecular form of somatostatin in the stomach, duodenum, and pancreas of rat and man (24–28). There is an increase in the relative proportion of S28 in the remainder of the small intestine.

METABOLISM

The half-life of S14 in plasma is extremely short, ranging from 0.5 to 3.0 min (29–35). In contrast, the plasma half-life of S28 has been found consistently to be two to five times longer (31, 33, 35). These results have led to confusion in estimating the relative potency of the two moieties. Many sites for degradation of somatostatin have been proposed, including liver (36, 37), pancreas (38), lungs (39), and kidneys (40). Recent studies have demonstrated rapid degradation of somatostatin by capillary aminopeptidases on isolated bovine brain microvessels (42) and also by aminopeptidase and endopeptidase activity on plasma membrane vesicles prepared from pig small intestine cells (42). These observations provide a potential explanation for rapid metabolism of endogenous somatostatin released by brain neurotransmissions or from gut mucosa. The possibility of capillary peptidase activity in vessels outside the brain has not been studied.

REGULATION OF SOMATOSTATIN RELEASE

Elucidation of the mechanisms by which release of somatostatin is regulated has been confounded by a multitude of problems. When studied *in vivo,* measurement of somatostatin in plasma has posed many difficulties. Circulating plasma somatostatin is collected distant from the site of release and probably represents a mixture of somatostatin released from many sources rather than from a single site. Conversely, since somatostatin is such an evanescent peptide and since it may be released for a paracrine action, circulating levels may remain unchanged in spite of significant local release. One response to these considerations is to study somatostatin release in an isolated organ preparation. However, even in such a system there may be regional variations in release within the organ or other uncontrolled and conflicting influences. Consequently isolated cellular preparations have proved particularly useful in elucidating both the intricate balance of controls that order somatostatin release and the intracellular mechanisms by which these controls are exercised.

Table 1 lists some of the factors shown to influence gastrointestinal somatostatin release in various models. Somatostatin release in response to luminal stimuli is of particular interest. Many studies in animals and man have shown that luminal nutrients, fat, and protein in particular, almost invariably release somatostatin into portal blood or peripheral circulation (43–47). Both S14 and S28 are released. The sites of release are probably gastric and duodenal, while in the intact dog at least the pancreas does not appear to contribute (48). The mechanisms by which nutrients initiate or sustain somatostatin release have not been elucidated well.

TABLE 1. SUMMARY OF AGENTS THAT INFLUENCE GASTRIC SOMATOSTATIN RELEASE*

Stimulants	*Inhibitors*
Luminal factors	
HCl	$NaHCO_3$
Mechanical	Peptone
Casein	
Fat	
Glucose	
Circulating nutrients	
Free fatty acid	
Peptides	
Glucagon	Substance P
Secretin	Met-enkephalin
VIP	Dermorphin
GIP	Insulin
Calcitonin	PP
CGRP	GRP
Gastrin	
CCK	
Bombesin	
Neurotransmitters and amines	
Epinephrine	Acetylcholine
Norepinephrine	GABA
Dopamine	Serotonin
Nucleotides and prostaglandins	
Cyclic AMP	
Prostaglandin E_2	
Drugs	
Theophylline	
Tolbutamine	
TPA	
Diacylglyceride	
Dimethyl-phenyliperazinium	

*From reference 66.

One possibility is that nutrients stimulate acid secretion, which in turn stimulates somatostatin release. Since somatostatin may act as an inhibitor of acid secretion, this would constitute a negative-feedback loop. However, although acid in many circumstances can stimulate somatostatin secretion (49, 50), this is not invariable (51). Since neutral solutions of nutrients can stimulate somatostatin release in antrectomized dogs (43), it is likely that nutrients can stimulate somatostatin independently of acid secretion. Thus the physiological importance of luminal acidity in somatostatin release is uncertain.

Somatostatin release stimulated by luminal nutrients is under neural control. However, *in vivo* and *in vitro* studies directed at defining these neural influences have yielded conflicting results. For example, in man and in intact dogs (52, 53), vagal tone appears to facilitate somatostatin secretion, while in intact cats (54), in isolated stomach, and isolated pancreas preparations cholinergic agonists are inhibitory (55–58). Similar conflicts are found with other neuropharmacologic agonists and antagonists.

Studies using an isolated cell culture system have allowed careful dissection of some of these influences. This technique achieves an enriched primary culture of somatostatin cells derived from canine fundic mucosal cells (59, 60). Canine fundic mucosal cells are dispersed with collagenase and then separated with counterflow elutriation. Following this process, somatostatin cells comprise about 9% of total cells in the small cell fractions and are separated completely from parietal cells and partially from chief and mucosa cells. Mast cells and other endocrine cells are also present. These small cell fractions are then plated onto collagen and maintained in primary culture for two days, after which somatostatin cells comprise 70 ± 6% of cultured cells. These cells can then be subjected to short-term incubation with neuropharmacologic agents and somatostatin release estimated.

Using this primary culture of enriched canine fundic D cells, at least two stimulatory pathways for somatostatin have been defined (59–63): a cAMP-dependent system and a cAMP-independent system (Figure 3). The cAMP-independent pathway may involve membrane phosphoinositide turnover and/or intracellular protein kinase C activation. It is partially dependent on extracellular calcium but appears to be unaffected by specific antagonists of membrane calcium channels or calmodulin. Epinephrine and beta-adrenergic agonists activate the cAMP-dependent system. Gastrin, CCK, and TPA (12-*O*-tetradecanoylphorbol-13-acetate, a phorbol ester that interacts directly with protein kinase C) activate the cAMP-independent pathway. It is of interest that CCK, on a molar basis, is a more potent stimulus of somatostatin release by these primary cultures than gastrin, although this greater potency does not correspond to great receptor affinity (61).

The inhibitory control of somatostatin release from primary cultures of enriched canine fundic D cells is complex. Under standard conditions carbachol reduces both basal and stimulated somatostatin release (60). The focus for this action appears to be distal to "second messengers," since carbachol inhibits the response to a diverse set of stimuli including epinephrine, dibutyryl cAMP, forskolin, gastrin, or TPA. It is curious, however, that while carbachol induces cAMP production, concomitantly it induces an increase in the indices of membrane inositol phospholipid turnover (63–65). These

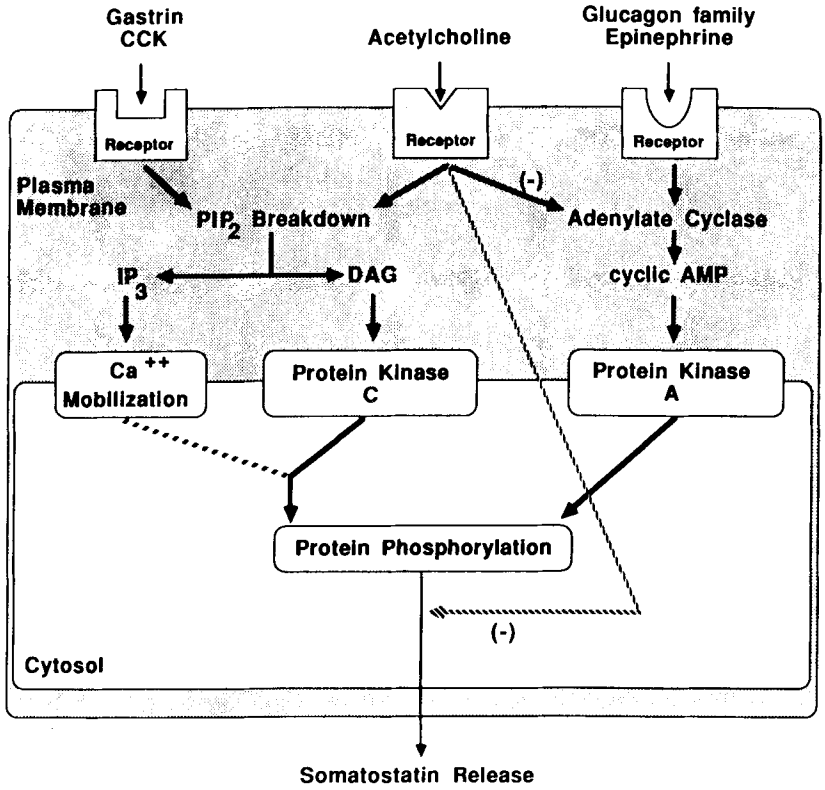

Fig 3. Intracellular mechanisms governing somatostatin release. CCK, cholecystokinin; DAG, diacylglycerol; IP_3, inositol triphosphate; PIP_2, phosphatidylinositol-4,5-bisphosphate (from reference 66).

conflicting observations were reconciled after further studies in which primary cultures of fundic D cells were pretreated with pertussis toxin prior to administration of carbachol. Pertussis toxin binds inhibitory guanine nucleotide-binding proteins regulating adenylate cyclase activity. Following pertussis toxin pretreatment, carbachol had a stimulatory effect on basal somatostatin release and potentiated the stimulatory response to forskolin (64). Pretreatment with pertussis toxin abolished the carbachol-induced decrease in cAMP production, but the increase in membrane inositol phospholipid turnover was unchanged. Atropine reversed all effects of carbachol in pertussis-toxin-pretreated D cells. These data suggest that in primary cultures of enriched canine fundic D cells carbachol interacts with a surface muscarinic receptor to have dual but contrary effects via separate intracellular mechanisms. First there is an inhibitory effect that is dependent in part on regulation of cAMP and that incorporates a pertussis-toxin-sensitive guanine nucleotide-binding protein. This action is dominant and only when it is inhibited by pretreatment with pertussis toxin is a second, albeit stimulatory, action of carbachol revealed. The stimulatory effect is complex and probably is not solely dependent on increases in membrane phosphoinositide turnover since carbachol, in the presence of pertussis toxin, can potentiate the release of somatostatin induced by gastrin without further enhancing phosphoinositide turnover (65).

ACTIONS OF SOMATOSTATIN IN THE GUT

A recurring problem in estimating the actions of somatostatin has been an inability to distinguish between physiological and pharmacological effects. While it is relatively easy to mimic physiological plasma concentrations of somatostatin, appropriate doses to mimic paracrine concentrations are rarely, if ever, known. It is possible that grossly pharmacologic doses of somatostatin yield concentrations that are physiologic at the cell surface.

Table 2 lists the proposed functions of endogenous somatostatin in the gastrointestinal tract. These have recently been reviewed (66). The action

TABLE 2. BIOLOGICAL ACTIONS OF SOMATOSTATIN IN THE GUT*

Inhibition of exocrine secretion
Stomach
acid
pepsinogen
Pancreas
digestive enzymes
bicarbonate
Liver
bile acid-independent bile flow
ductular secretion
Salivary gland
amylase
Inhibition of neuroendocrine secretion
Gastrointestinal tract—gastrin, CCK, secretin, VIP, GIP, motilin, gut glucagon, EGF, acetylcholine
Pancreas—insulin, glucagon, pancreatic polypeptide
Motility
Inhibition
late phase of gastric emptying
gastric MMCs
gallbladder contraction
ileal longitudinal muscle contraction
Stimulation
early phase of gastric emptying
intestinal MMCs
Intestinal Transport
Inhibition
secretion of fluid and bicarbonate
absorption of calcium, glucose, glucatose, glycerol, fructose, xylose, lactose, amino acids, triglycerides
Miscellaneous
Inhibition of splanchnic blood flow
Inhibition of tissue growth and proliferation
Food intake
stimulation in fasted animals
inhibition in fed animals

*From reference 66.

of gut somatostatin that has received most attention is regulation of acid secretion. In both dogs (33) and man (45) *in vivo* it has been shown that a physiological increase in plasma somatostatin concentration, such as occurs postprandially, can result in reduction in acid secretion. This occurs without an alteration in plasma gastrin concentration. This suggests that somatostatin may circulate to act as an endocrine regulator of acid secretion. In the dog S14 is 10 times as potent an inhibitor of acid secretion as S28 (33). This became clear only after their different rates of metabolism were taken into consideration and their respective potencies examined as a function of incremental plasma concentration.

Recently Seal et al (67) have shown in rats with a gastric fistula that intravenous administration of a specific monoclonal antisomatostatin antibody can reverse the inhibitory action of intraduodenal infusion of oleic acid on meal-stimulated gastric acid secretion. This suggests that the acid inhibitory action of intraduodenal fat (so-called enterogastrone effect) is at least in part a consequence of the action of endogenous somatostatin. Whether this is an endocrine or paracrine phenomenon needs further study.

As noted earlier in this review, the morphology of gastric D cells with long cytoplasmic processes abutting onto local effector cells suggests a paracrine role for gastric somatostatin. Short et al (68) have reported that perfusion of an isolated rat stomach with antisomatostatin antibody enhanced acid secretion. Thus, locally released somatostatin may be acting as a restraint on acid secretion.

There are many mechanisms by which somatostatin might reduce acid secretion. As shown in Table 3, these include direct action on the parietal cell, inhibition of gastrin release, increased production of prostaglandins, and reduction in mucosal blood flow. It is most likely that somatostatin produces its effect on acid secretion by a combination of actions.

The advent of stable somatostatin analogs for use as radioligands has allowed demonstration of surface receptors for somatostatin on isolated enriched canine parietal cells in short-term culture (69). In this model, binding affinity closely parallels the inhibitory potency of the peptide. However, the equal potency of S14 and S28 observed in this model is in sharp contrast to the markedly greater potency of S14 compared to S28 *in vivo*. This suggests that indirect influences may be of great importance in determining the acid inhibitory action of circulating somatostatin. Although there are differences in their data, both Park et al (69) and Chew (70) have been able to demonstrate a direct effect of somatostatin on function in isolated parietal cells.

The influence of somatostatin, if any, on gastrin secretion is most likely to be paracrine since plasma concentrations of somatostatin sufficient to inhibit

TABLE 3. MECHANISMS OF SOMATOSTATIN-INDUCED ACID INHIBITION*

Receptor	?	?	Gastrin cell	Parietal cell
Effects	↓ Blood flow	↑ Prostaglandin	↓ Gastrin release	↓ Gastrin/acetylcholine effect
	↓ O_2	↓ Histamine effect	↓ Stimulation	↓ Stimulation
Mechanism	↓ Metabolic function	↓ Protein kinase A	↓ Protein kinase C	↓ Postkinase activation action

*From reference 66.

acid secretion completely had no effect on serum gastrin. The morphology of D cells in the antrum supports this mechanism of action. Much work has been directed at defining the exact interrelationship of gastrin and somatostatin. In many instances the secretion of the two peptides appears reciprocal, demonstrating a so-called functional linkage, but this is not invariable. Nonetheless, local regulation of gastrin by somatostatin appears probable.

CELLULAR BASIS OF SOMATOSTATIN ACTION

In order to consider the cellular mechanisms by which somatostatin exerts its actions, one must frequently extrapolate from studies in nongastrointestinal systems. These studies, as well as studies in cells of gastrointestinal origin, suggest that somatostatin may have many effects. Somatostatin has been shown to interfere with cAMP production in primary cultures of enriched parietal cells through inhibition of adenylate cyclase (69). This action (and some others described below) may require interaction with a membrane-associated guanine nucleotide regulatory protein. Somatostatin may also inhibit parietal cell function by interfering with a cAMP-related pathway at a point distal to cAMP production or through cAMP-independent mechanisms (69). In nongastrointestinal D cells it has been proposed that this pathway is also related to a membrane-associated pertussis-toxin-sensitive guanine nucleotide-regulating protein (71). There are conflicting data regarding the role of intracellular calcium fluxes in modulating the cAMP-independent pathway. Somatostatin may act through a more nonselective mechanism such as that proposed by Reyl and Lewin (72), who showed that the intracellular binding site for somatostatin in gastric mucosa may be a phosphoprotein phosphatase. It has been suggested that somatostatin alters membrane-related events, such as dephosphorylating membrane proteins (73), or alters the final exocytic process (74). By whatever mechanism somatostatin acts, its physiological importance as a regulator of many processes in the body is profound. The potential usefulness of an analog of this interesting hormone in therapy of a variety of human pathological conditions will soon be explored.

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