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Progress report

Endogenous somatostatin and the gut

Somatostatin is a naturally occuring polypeptide first discovered in porcine hypothalamini by Brazeau *et al*[1] in 1973 after original observations by Kruhlich *et al*.[2] It has been identified in many mammalian tissues especially brain, gut, and pancreas. The molecular form first described consists of 14 amino acids in a cyclic arrangement and is called somatostatin-14. (Fig. 1). Precursor forms of larger molecular weight have since been recognised. Somatostatin-28, also called prosomatostatin, is a 28 amino acid polypeptide and includes the complete somatostatin-14 at its N terminus.[3] (Fig. 2). Preprosomatostatins are polypeptides of 120 or more amino acids and usually contain the somatostatin-28 sequence at the C-terminus.[4 5] When infused in pharmacological doses into animals or man somatostatin-14 inhibits many endocrine and gastrointestinal functions.[6] Somatostatin-28 is also a pharmacological inhibitor although it can differ from somatostatin-14 in specific effects.[7 8]

Four interrelated functions have been proposed for endogenous somatostatin: (a) neurohumeral regulator, (2) neurotransmitter (3) endocrine hormone and (4) paracrine hormone. There is strong evidence that

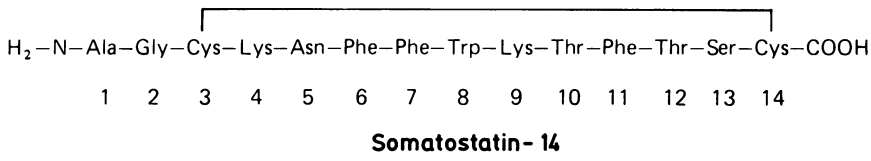

Fig. 1 *Amino acid sequence of somatostatin-14.*

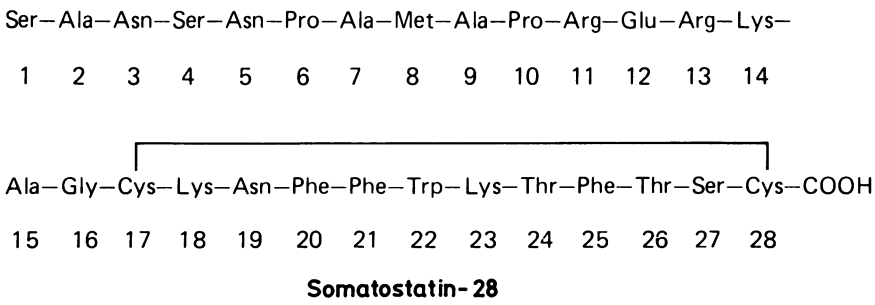

Fig. 2 *Amino acid sequence of somatostatin-28.*

endogenous somatostatin is a neurohumeral regulator of secretion by the anterior pituitary gland of growth hormone and probably thyroid stimulating hormone[9]; and that somatostatin acts as a peptidergic neurotransmitter in autonomic nerves.[10 11] For further discussion of these actions of endogenous somatostatin and also the controversies surrounding the proposed physiological functions of somatostatin in the endocrine pancreas, the reader is referred to the review by Reichlin.[9] This progress report will describe the mechanism of action, the distribution, release, and metabolism of somatostatin in the gut with particular reference to recent studies in man and consider current hypotheses on the possible endocrine and paracrine roles of gastrointestinal somatostatin.

Mechanism of action of somatostatin

The actions of somatostatin which have been most extensively studied are inhibition of release growth hormone and of insulin. It is uncertain whether mechanisms defined in the somatotroph and pancreatic islet can be extrapolated to gut and neural tissue. Somatostatin acts by binding with plasma membrane receptors. These high affinity binding sites have been identified on cultured anterior pituitary cells,[12] on pancreatic cells[13] and on adipocytes.[14] Furthermore, they have been found on secretory vesicles isolated from anterior pituitary cells[14] and pancreatic islets.[14] The presence of somatostatin receptors on intracellular organelles might suggest an intracellular site of action. Mehler *et al* have shown, however, that somatostatin binding by islets is enhanced in the presence of substances such as glucose which are known to promote secretory vesicle migration and insulin release.[15] This results from increased receptor concentration independent of protein synthesis and the authors cautiously suggest that it is caused by increased migration of receptors to the cell surface.[16] Thus in pancreas and pituitary at least the secretory vesicle may serve a dual role of carrying to its cell surface both its stored peptide and somatostatin binding sites, thereby assisting in a feedback control mechanism. Consequent on somatostatin binding to receptor sites there may be an inhibition of calcium dependent secretory processes either by alteration of calcium influx into the cell[17] or by disturbing translocation from bound to free calcium within the cell[18] or by some disturbance of the intracellular responses to such events.[18] One of these steps in the process may be inhibition of cyclic AMP-stimulated protein kinase,[19] but direct disturbance of cyclic nucleotide concentration does not seem likely.[20 21]

Distribution of somatostatin in the gastrointestinal tract

The gastrointestinal tract and pancreas contain the greatest amounts of somatostatin in mammals.[22] Whether estimated per wet weight of tissue or by counting regional distribution of somatostatin endocrine cells, somatostatin is most abundant within the human gut in the stomach duodenum and jejunum, with decreasing amounts in the ileum and colon.[23 24] Chromatographic studies show that the predominant form of somatostatin in human stomach and duodenum coeluts with somatostatin-14 while there is a relative increase in the proportion of a somatostatin-28 like form further down the gastrointestinal tract.[24] Similar results are reported in rat

intestine.[25] More than 90% of the somatostatin immunoreactivity in human gut is confined to the mucosal layer where it is localised to endocrine cells termed D cells.[24] The remainder of somatostatin immunoreactivity in human gut is present in neural tissue within the muscle coat.[24] In both rat and man some gastric D cells possess cytoplasmic extensions which contain somatostatin storage granules. In the rat these processes terminate on putative effector cells such as gastrin cells, parietal cells, chief cells and cells staining for histamine or serotonin.[26] Similar processes have been seen in some small intestinal somatostatin cells in the rat, although other rat small intestinal somatostatin cells possess the classical flask shape of endocrine epithelial cells.[26]

The human pancreas is abundant in somatostatin[24] which is localised in endocrine D cells at the periphery of the islets of Langerhans.[26] Somatostatin containing endocrine cells have been identified in the extrahepatic biliary tract but not gall bladder in man.[27] Somatostatin cells have not been identified within the liver parenchyma.

Release of circulating somatostatin

Caution must be exercised when interpreting studies of endogenous circulating somatostatin. It is difficult to measure endogenous somatostatin in plasma because it is present in very low concentrations. Furthermore, plasma causes variable interference with binding of antisomatostatin antibody to radiolabelled somatostatin tracer in most radioimmunoassays.[28 29] This necessitates extraction of somatostatin from plasma before assay.[28 29] Many antibodies do not distinguish between somatostatin-14 and larger molecular weight forms. Despite these caveats a consistent pattern of release of endogenous plasma somatostatin in man can be defined.

Endogenous somatostatin is released into the peripheral circulation in man by oral ingestion of food,[30 31] particularly fat and protein,[32] by intraduodenal infusion of nutrients of which fat is the most potent,[33] and by intravenous infusion of arginine.[34] Intravenous free fatty acids, but not fat emulsion, stimulate the release of plasma somatostatin in dogs[35] and man.[36] The postprandial rise in circulating somatostatin in man is due to release of both somatostatin-14 and somatostatin-28.[32 37]

Insulin induced hypoglycaemia is followed by a rise in circulating somatostatin concentrations in man.[38] Gastric acid, however, does not appear to be a major direct stimulus of circulating somatostatin in man.[39] Direct infusion of moderate doses of hydrochloric acid into the stomach or duodenum in normal man does not raise circulating somatostatin concentrations while even with grossly supraphysiological intraduodenal infusion of hydrochloric acid the rise in circulating somatostatin concentrations is submaximal.[39] This is in contrast with the reported release of somatostatin by intraluminal acidification in dogs.[40] These species differences in data from dogs and man indicate hazards in extrapolating the results of animal studies to man.

The exact source or sources of the circulating somatostatin which is released in man by enteral or intravenous stimuli is uncertain, as blood samples cannot be drawn directly from vessels draining somatostatin rich tissues. It is most likely, however, that the upper gastrointestinal tract and pancreas are the major sources. Furthermore, animal experiments suggest

that when nutrients are placed locally into the stomach or duodenum, somatostatin is released from the stomach duodenum and pancreas in concert and not solely from the site of contact.[40]

Release of circulating somatostatin is under neurological control. Atropine attenuates the circulating somatostatin response in man to both orally ingested food and intraduodenal fat, suggesting that the vagus nerve has an important role mediating circulating somatostatin release in man.[41] Further evidence of vagal control of circulating somatostatin release is the rise in plasma somatostatin after insulin-induced hypoglycaemia,[38] a known vagal stimulus. This response to hypoglycaemia is absent in vagotomised subjects[42] and diabetic subjects with autonomic neuropathy.[43] Neither alpha-adrenergic nor beta-adrenergic blockade has been found to reduce the postprandial release of circulating somatostatin in man,[41] although beta-adrenergic blockade has been reported to attenuate the circulating somatostatin response to intravenous infusion of free fatty acids.[36]

In both dogs[44] and man[31] the opiate antagonist naloxine attenuated the circulating somatostatin response to oral food. This implies that endogenous opiates are factors mediating the postprandial release of somatostatin. Although pharmacological infusions of many regulatory peptides are reported to stimulate somatostatin release *in vivo*[45 46] it is uncertain whether any of these interactions are mirrored in normal physiological function. The putative local interaction in the stomach and small gut of somatostatin with gastrin, gastrin releasing peptide, motilin, and possibly secretin and VIP will be discussed below. Current evidence indicates that endogenous prostaglandins do not participate in postprandial release of circulating somatostatin in man.[47]

Release of luminal somatostatin

Secretion of endogenous somatostatin directly into the intestinal lumen is described in cats,[48] dogs[49] and rats.[50] In these models electrical stimulation of the vagus nerve results in secretion of somatostatin. In rats, maintenance of a low intragastric pH although not itself a potent stimulus of intraluminal somatostatin release, appears to facilitate vagal stimulation.[50] Pentagastrin has been reported to raise the somatostatin content of gastric juice in man.[51]

Metabolism of somatostatin

The half life in plasma of exogenous somatostatin-14 is estimated to range from 0·57 to 1·8 minutes in dogs,[52–54] 2·4 minutes in cats[55] and 1·1 to 3·0 minutes in man.[56] The plasma half life of somatostatin-28 is consistently longer than that of somatostatin-14 in rat,[57] dog,[52] and cat.[55] Many sites of metabolism of somatostatin have been proposed. Extracts of rat brain[58 59] and rat and human serum[60] can degrade somatostatin by means of endogenous peptidases. A transhepatic gradient in plasma somatostatin has been described in man.[61] Significant hepatic clearance of exogenous somatostatin-14 has been reported in dogs,[62] rats,[63] and cirrhotic men[64] although one group failed to show this in dogs.[53] The canine pancreas extracts significant amounts of exogenous somatostatin-14.[65] In this regard

it is interesting that Webb and her colleagues reported a gradient in plasma somatostatin concentrations across the splanchnic vascular bed during an infusion of exogenous somatostatin-14 in cirrhotic men.[64] This also could represent pancreatic extraction. Thus it is likely that somatostatin released into the portal blood stream is metabolised by the pancreas, liver, and by endogenous plasma peptidases.

There is a transrenal gradient of plasma somatostatin in the rat.[66] Further evidence of renal excretion of endogenous somatostatin is the delayed clearance of somatostatin in chronic renal failure.[56] The lung is not a site of metabolism of somatostatin in man.[64]

Physiological functions of gastrointestinal somatostatin

CONTROL OF GASTRIC ACID SECRETION

Endogenous somatostatin may influence gastric acid secretion both directly by acting on the parietal cell and indirectly by regulating gastrin secretion. The evidence for a direct role for somatostatin is circumstantial. Food and insulin induced hypoglycaemia are potent stimuli of gastric acid secretion[67] and circulating somatostatin in man.[30 38] Exogenous somatostatin-14 even in low doses inhibits gastric acid secretion in dogs[52] and man,[68] probably by a direct effect on the parietal cell.[69] Thus when endogenous somatostatin and gastric acid are secreted contemporaneously, somatostatin may be acting as a physiological restraint against excessive acid secretion. It is likely that paracrine somatostatin is an episodic rather than continuous regulator of acid secretion. Eklund *et al* have described tachyphylaxis of acid secretion to exogenous intravenous somatostatin in an *in vivo* rat stomach model.[70] Whether regulation of acid secretion is solely a function of locally released somatostatin or a true endocrine effect of circulating somatostatin is uncertain. The recent studies of Colturi and colleagues, however, do suggest such an endocrine effect of circulating somatostatin.[68] These workers showed that when exogenous somatostatin-14 is infused in man in doses which stimulate postprandial circulating levels there is a 48% reduction in basal acid output, without an accompanying reduction in serum gastrin levels.[68] Similarly the observation that fat is the most potent intraduodenal nutrient stimulus of circulating somatostatin has led the present author to suggest that circulating somatostatin is an enterogastrone – a circulating hormone released by intraduodenal fat which inhibits acid secretion.[33] It is possible also that somatostatin released into the stomach lumen might act to control acid secretion. It is reported that infusion of exogenous somatostatin-14 into the stomach of normal human subjects inhibited acid secretion.[71] This requires further study.

The evidence that locally released endogenous somatostatin is intimately involved in regulating gastrin release is largely derived from *in vitro* animal experiments, particularly those utilising an isolated rat stomach. As already described gastric somatostatin D cells give out cellular extensions containing somatostatin granules, which abut onto gastrin cells.[26] Saffouri and coworkers have shown that perfusion of an isolated rat stomach preparation with antisomatostatin antiserum stimulates gastrin release.[72] In the same model cholinergic agonists stimulate gastrin and inhibit somatostatin release while atropine inhibits gastrin and stimulates somato-

statin release.[73] These workers propose a 'functional linkage' of gastrin and somatostatin in which somatostatin is a cholinergically mediated paracrine restraint of gastrin release.[73] It is emphasised that these data relate to an *in vitro* rat stomach model. Whether a similar paracrine functional linkage of somatostatin and gastrin occurs in human stomach is unknown. It should be noted, however, that the effects of atropine on postprandial levels of circulating somatostatin and gastrin in man differ from the responses of these peptides to perfusion of atropine in the isolated rat stomach. In man atropine attenuates postprandial plasma somatostatin while enhancing postprandial plasma gastrin.[41]

Gastrin releasing peptide (GRP) or its close homologue the frog polypeptide bombesin also participates in this regulatory mechanism in the isolated rat stomach.[74] It is present within nerves in many mammalian gastrointestinal tissues,[75] including human stomach.[76] Vagal stimulation of porcine stomach stimulates GRP release.[77] Bombesin is a potent exogenous stimulus of gastrin release in man.[78] In the isolated rat stomach perfusion with bombesin stimulates gastrin and somatostatin release.[74 79] When this model is perfused with bombesin plus antisomatostatin antiserum, gastrin release is greatly augmented.[74] Thus it is proposed that GRP/bombesin is the local positive stimulus and somatostatin the local negative stimulus of the parietal cell.[74] (Fig. 3). Furthermore in a complex system of intramural checks and balances GRP/bombesin may simultaneously stimulate local release of somatostatin.

It has been suggested that other locally released polypeptides such as secretin and possibly its homologues VIP and GIP may also be involved in this regulatory system.[80] Saffouri *et al,* however, could not substantiate this in the isolated rat stomach.[81]

CONTROL OF INTESTINAL FUNCTIONS

The infusion of pharmacological doses of somatostatin-14 lowers the

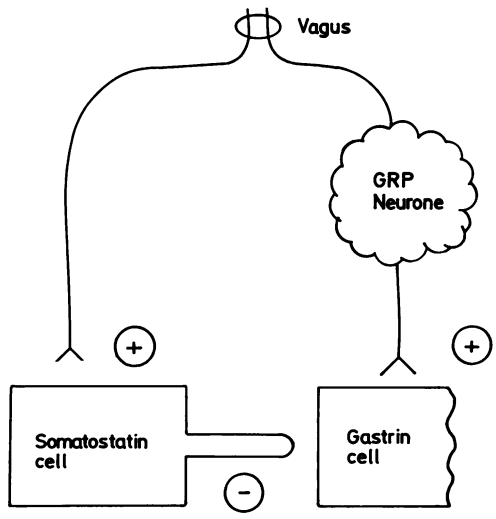

Fig. 3 *Proposed paracrine control of gastrin secretion (after Duval et al*[74]).

absorption of orally administered glucose,[82] xylose,[82] calcium,[83] protein,[84] and fat.[85] Consequently although the above mentioned data all refer to pharmacological effects of somatostatin, it has been suggested that endogenous somatostatin exerts control over nutrient influx in man. This may be particularly so for fat absorption in view of the potency of intraduodenal fat as a stimulus of circulating somatostatin.[33] Furthermore it is reported that neutralisation of endogenous somatostatin by administration of antisomatostatin antiserum to dogs significantly increases postprandial plasma triglyceride.[86]

Another mechanism whereby endogenous somatostatin might influence nutrition is by mediating satiety and thereby food intake.[87 88]

Endogenous somatostatin may also play a role in regulating gut motility. Peeters and coworkers have reported a consistent rise in circulating somatostatin concentrations before the onset of either spontaneous fasting or motilin induced migrating motor complexes in normal subjects.[89] Although exogenous somatostatin can alter such parameters as fluid and electrolyte movement in the intestine[90 91] and bile flow[92 93] there is as yet no convincing evidence that endogenous somatostatin serves such a physiological role.

Conclusion

It is clear that endogenous somatostatin is present in man in the stomach, upper small gut, and pancreas, that it is released into the peripheral circulation by food given orally or intraduodenally and that this release is under vagal control. Studies of gastric physiology *in vivo* and *in vitro* strongly suggest that endogenous somatostatin is an important paracrine inhibitor of gastrin secretion and also that circulating somatostatin probably has a true endocrine function acting directly on the parietal cell to inhibit acid secretion. The implication of endogenous somatostatin in regulating other gastrointestinal functions such as nutrient influx, gut motility and fluid and electrolyte movement is less well established and requires further study. Lest this appear a daunting task it is worth recalling that more than 80 years have passed since the discovery by Bayliss and Starling of secretin,[94] the first hormone, and yet many unanswered questions remain about its physiological roles. The growth in our knowledge of gastrointestinal somatostatin parallels the growth of understanding of many regulatory hormones in the gut and signposts exciting discoveries ahead.

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