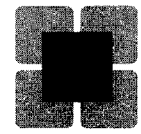

Octreotide: a hormone for all diseases?

SOMATOSTATIN appears to play many neuroendocrine, endocrine, and paracrine roles in normal physiology; indeed, it has been suggested that it also acts within the gut lumen as a "lumone" to regulate absorption processes.[1] The documented effects of somatostatin, achieved by local secretion through portal, neural, or interstitial delivery systems, include regulation of normal gut motility; secretion and inhibition of insulin, glucagon, growth hormone (GH) and thyroid-stimulating hormone (TSH) secretion. The role of *systemic circulating somatostatin*, however, has not been clearly described.

When somatostatin is administered intravenously, a wide spectrum of pharmacologic effects also occurs, including potent inhibition of pancreatic exocrine secretions, decrease in splanchnic blood flow, biliary stasis, and inhibition of the secretion of gastrin and gastric acid. Somatostatin probably plays a physiologic role in these cases as well. Prolonged exposure to pharmacologic concentrations of somatostatin occurs when the rare somatostatinoma islet-cell tumor is present and is associated with weight loss, malabsorptive diarrhea, diabetes, and gallstones.[2]

■ *See Camisa et al (pp 71–76 and 77–81)*

A pharmacologically useful congener of somatostatin has been the object of a long search. Octreotide, formerly called SMS 201-995, is a long-acting somatostatin analog that is administered parenterally.[3] Although somatostatin analogs were developed with the hope that they could be used selectively, octreotide appears to encompass the full spectrum of somatostatin's actions if given in high enough doses.[4] Major side effects of prolonged treatment with octreotide are mild fat malabsorption, glucose intolerance, biliary stasis, and gallstones. However, gallstones and significant malabsorption have occurred rarely, and most patients receiving octreotide have not suffered significant adverse consequences even after several years of therapy.[5]

SELECTIVITY AND THERAPEUTIC USE

Octreotide is the first clinically useful analog of somatostatin because of its prolonged half-life (110 min) after subcutaneous injection. It is usually administered two to three times daily or by continuous (pump) infusion, and the duration of effect varies with the clinical situation. In pathologic situations, octreotide has shown a remarkable selectivity for tumors that secrete excessive quantities of hormone, such as pituitary tumors secreting GH or TSH; islet-cell tumors secreting ectopic hormones such as vasoactive intestinal peptide (VIP), gastrin, growth hormone releasing hormone (GHRH), or adrenocorticotrophic hormone (ACTH); and carcinoid tumors.[4] In the presence of carcinoid syndrome, VIP-induced secretory diarrhea (pancreatic cholera), and TSH-secreting tumors, octreotide is clearly the best available agent to control the effects of excess hormone secretion. The Food and Drug Administration has approved the drug for use in the first two instances.

In addition, octreotide has been found to block "carcinoid crisis," which is the sudden massive release of serotonin and other peptides from carcinoid tumors, typically in response to induction with anesthesia.[6] In acromegaly, the analog is probably better tolerated and more potent in suppression of GH release than bromocriptine, although this use has not been approved. In all these cases, octreotide has dramatic effects, inhibiting tumoral hormone release without major disruption of normal physiology. For an analog of somatostatin, this implies a high degree of therapeutic selectivity. However, the tumors that secrete hormones appear to be supersensitive to somatostatin relative to normal tissue. This may be due to expression of excess somatostatin receptors by the tumors or the selectivity of somatostatin

for stimulated secretory mechanisms. When given to normal volunteers, octreotide has only minimal effect on basal levels of GH or TSH but abolishes release of the hormones after administration of their respective releasing factors.[4]

Similarly, while there are moderate effects on basal insulin and glucagon, the release of these hormones after stimulation, such as after eating, is markedly blunted. In addition, octreotide has been reported to control postprandial hypotension, a syndrome that may be due to excessive release of gastrointestinal hormonal factors.[7] If one regards tumoral hormone production as a constitutively stimulated secretory state, then octreotide appears to be selective for blockade of stimulated hormone release.

Is octreotide useful in diseases in which there is no excessive, stimulated, or tumoral hormone release? Octreotide has been used in diabetes to attempt to reduce relative hyperglucagonemia; however, the clinical impact on glycemia has been modest.[8] Large trials of octreotide therapy to control acute pancreatitis or gastrointestinal bleeding have not shown clinical benefit. Recent data indicate that octreotide may be used beneficially to reduce flow rates and promote closure due to pancreatic fistulas.[9] Nonetheless, most reports of clinical success involve therapy for hormone-excess syndromes.

OCTREOTIDE AND PSORIASIS

The first paper by Camisa et al describes a trial of octreotide for psoriasis. In an uncontrolled open-label study, the investigators noted some improvement in the severity but not the extent of psoriatic lesions in six of nine patients. Although the initial rationales for octreotide use were previous results with somatostatin and the hypothesis that psoriatic lesions were dependent to some extent on the GH/somatomedin C (Sm-C) hormone system, the authors were unable to demonstrate effects at GH or Sm-C levels. In the second paper, involving the same patients, stimulated insulin, pancreatic polypeptide, and nocturnal TSH levels were blunted by octreotide, but not glucagon or iodothyronines. Therefore, a clinical effect, albeit modest, was noted, but the mechanism of the effect is obscure. Octreotide may be acting on a previously unknown hormonal system involved in psoriasis or on the epidermal cells themselves. It is worthwhile to point out that octreotide effectively clears the rash of glucagonoma and simultaneously increases serum alanine levels without a sustained decrease in glucagon levels.[10] Thus, octreotide may have effects on hormone systems within the epidermis or a systemic hormone system linking amino-acid metabolism and skin lesions. It would be of interest to know if Camisa et al noted any alteration in serum amino acids.

SITE OF ACTION

The fact that Camisa and colleagues observed clinical benefit without effects on the GH/Sm-C hormone system raises an important issue involving clinical research with octreotide: where does the analog act in disease states responsive to it? Even in well-understood systems, the locus of octreotide effects is obscure. In VIPoma, tremendous clinical benefit is observed without reducing VIP to normal levels. In TSH- and GH-secreting tumors, clinical benefits or reduction in secondary hormones (Sm-C) are occasionally observed without reduction in TSH or GH.[4] Effects on symptoms often precede demonstrable hormonal effects. There are numerous reports of relief of headache and joint pain in acromegaly before significant reduction in GH. These clinical observations have several interesting possible explanations:

1. Decreased sensitivity of target organs exposed for prolonged periods to excess hormone levels so that small reductions in excessive VIP or GH have major symptomatic effects,
2. Direct effects on targets such as the thyroid gland, joints, or gastrointestinal system independent of effects on hormone secretion, and
3. Measurement of the wrong hormone, ie, using GH as a marker for effects on acromegaly when octreotide has actually been clinically effective by simultaneously reducing another hormone.

APPLICABILITY

How widely applicable is octreotide in clinical therapy? It is clear from the basic and clinical research of the past two decades that cells "communicate" with each other by a variety of hormone systems, from the self-contained portal systems of the pituitary hypothalamus to the lymphokine system that permits the immunologic "organ" to be diffused throughout the body. Many peptides and other substances have been and will be discovered that act locally in a paracrine manner on neighboring cells to maintain growth, to alter functional relationships, etc. If somatostatin regulates any or all of these secretory systems, octreotide may have important effects on many diseases.

For example, octreotide may be useful in the control of tumor growth. It has been reported to decrease the

size of pituitary, islet-cell, and carcinoid tumors to varying degrees.[4] Because endocrine tumors grow slowly, they are not likely to provide a good test of the growth-inhibiting effects of octreotide. Also, effects on endocrine tumors have not always been sustained or predictable; a recent review of the data suggests a 30%–50% decrease in tumor size has been observed in 20%–30% of patients.[4] Although these data do not support use of the analog solely to reduce tumor size, Barkan et al[11] have indicated that small octreotide-induced reductions in the size of nonirradiated pituitary tumors may be more predictable and may facilitate surgical removal. On a broader level, many cells in culture are believed to sustain growth by secreting growth factors into the media that bathes them (an "autocrine" mechanism). If tumor growth is suspected to be sustained on an endocrine or autocrine basis, particularly in tumors with rapid growth characteristics, trials of octreotide are warranted. As another example, because the immune system is dependent on hormonal communication, investigation of somatostatin or octreotide effects could lead to a large number of possible applications in clinical therapy.

FUTURE DIRECTIONS

How can one focus studies of an agent with such broad activity and possible loci of action? If one focuses on the single documented selective aspect of somatostatin action, namely, blockade of stimulated hormone release, then demonstration of efficacy in a clinical syndrome may be taken as evidence that the syndrome is based, in part, on a stimulated hormone system. In psoriasis, repeated studies have not shown stimulation (ie, increased levels) in the GH/Sm-C axis, and it is unlikely that somatostatin is acting through this system. The efficacy of octreotide in psoriasis should prompt a search for other activated hormone systems, perhaps via a paracrine mechanism. This can be done by investigating other hormones known to affect skin turnover, examination of psoriatic lesions for somatostatin receptors, or studies of primary cultures of tissue from plaques to attempt to identify secretion of hormonal substances. In syndromes such as postprandial hypotension, the efficacy of octreotide suggests that some factor released in response to meals is suppressed by somatostatin.

However, the most efficient investigation of octreotide as a clinical agent would begin with identification of a process dependent on stimulated hormone secretion and then ascertainment of the effects of the analog, as well as identification of somatostatin receptors on potential target cells.

SUMMARY

Octreotide is a new agent with many documented useful applications and a huge number of possible applications. Each documented therapeutic effect will require careful analysis. Particular care must be taken to design controls, use double-blind tests for objective study of subjective benefits, and frame questions to elicit precise answers. The most important guide is to keep an open mind when attempting to discern a mechanism of action.

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