Antibodies to Gastrin: Their Production and Significance

Through the elegant studies of Gregory and Tracy and their associates, we now appreciate that gastrin molecules, obtained from a variety of mammalian species, are 17-member single-chain polypeptide structures. Gastrin molecules from different species, analogous to previous investigations with insulin, were found to be nearly identical in structure. Most provocative was the observation that the carboxyl-terminal tetrapeptide amide contained all the physiologic properties of the intact hormone, though not in terms of equimolar potency.

When the primary structure of gastrin was recognized, a surge of interest developed in obtaining antibodies to gastrin molecules. The many applications of antibodies with specificity for gastrin are evident; principal among such applications would be the development of a sensitive immunoassay system for gastrin and the use of antibodies to localize gastrin within tissue sites. A description of the structure of gastrin comes at a time of enormous advances in the use of small peptides as antigens and heptenic determinants, and with the development of a wide variety of sensitive assay systems for measurement of peptide hormones.

Because of the apparent functional importance, and perhaps uniqueness, of the gastrin tetrapeptide, we produced antibodies to this portion of the gastrin molecule by immunization with the carboxyl-terminal tetrapeptide amide of gastrin covalently conjugated to carrier-protein molecules. Peptides of fewer than eight amino acid residues cannot serve as complete antigens, requiring a carrier of some variety, usually a macromolecule, to elicit an antibody response against the peptide. Antibodies thus obtained were found to bind equivalently on an equimolar basis the gastrin tetrapeptide, gastrin molecules and the peptide hormone cholecystokinin-pancreozymin found by Mutt and Jorpes to contain the same carboxyl-terminal tetrapeptide amide as gastrin.

In addition, we have produced antibodies to human gastrin. We chose to

From the Department of Medicine, Washington University School of Medicine, St. Louis, Mo. 63110.

Supported in part by Research Grant 1 RO1 AM 10837 and Research Career Development Award 7-K3-AI-19,499 from the National Institutes of Health, U. S. Public Health Service, by Grant T-394 from the American Cancer Society, and by Grant-In-Aid 66 679 from the American Heart Association.
couple the gastrin molecule to a carrier protein to enhance the immunogenicity of the peptide hormone. Both termini of gastrin molecules are blocked—the carboxyl-terminus by an amide group and the amino terminus by a cyclic pyroglutamyl residue. Therefore, human gastrin I, residues 2–17, with a free and potentially reactive N-terminal amino group, was coupled to a carried protein for immunization. The antibodies, obtained from rabbits, were used in the development of a sensitive radioiodine-immunoassay system. Antibodies to human gastrin I obtained in the same way, were used to measure gastrin levels in sera from patients with the Zollinger-Ellison syndrome and to compare these levels with those from patients without recognized gastrointestinal diseases. Greatly elevated levels of gastrin were found in the sera of patients with the Zollinger-Ellison syndrome, affording strong evidence that gastrin is indeed the circulating acid secretagogue in these patients.

Other methods also have been successful in producing antibodies with specificity for gastrin molecules. Schneider and his associates immunized rabbits with a partially purified gastrin preparation from porcine antral mucosa and were able to detect antibodies which reacted with human gastrin using a hemagglutination inhibition technic. Stremple and his colleagues produced antibodies with specificity for gastrin by immunizing chickens with negatively charged gastrin molecules bound to positively charged polyacrylate particles. They detected these antibodies using immunodiffusion in agar gel.

The availability of antibodies to gastrin affords us with an enormously powerful tool for application to a wide variety of important questions in normal gastrointestinal physiology and to the disordered physiologic states of certain gastrointestinal diseases. Antibodies to gastrin should allow us to probe the most interesting structure-function relationships between gastrin and cholecystokinin-pancreozymin. Antibodies to gastrin should allow us to examine more closely the role of gastrin in the physiologic control of gastric secretion. In the Zollinger-Ellison syndrome, are gastrin levels uniformly elevated in all patients? Are there substantial hour-to-hour and day-to-day variations in gastrin levels in these patients or are gastrin levels relatively constant? Is the liberation of gastrin from tumors of the Zollinger-Ellison variety subject to the usual control mechanisms associated with gastrin release or are these tumors functionally autonomous? What is the role of gastrin levels in patients with customary peptic ulcer disease and in duodenal ulcer disease vs. gastric ulcer disease? Will gastrin levels differ in patients with benign and malignant gastric ulcer? What of gastrin levels in patients with gastric atrophy, with or without pernicious anemia?

These few questions and the many others which come to mind bring into focus the potential usefulness of antibodies to gastrin. It is anticipated that many groups of investigators using antibodies to gastrin, the elicitation of such antibodies made possible by the enormously important structural work