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 I. We chose to...
couple the gastrin molecule to a carrier protein to enhance the immuno-
genicity 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. Anti-
bodies 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 gastro-
intestinal 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 polycrylate 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

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