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Cellular and Molecular Targets of Gastrin

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INTRODUCTION

Gastrin was recognized as a hormone that stimulates gastric secretion almost 60 yr ago. Its existence was proved by Komarov (1) in 1938. It was first isolated and characterized by Gregory and Tracy (2,3) in 1961, and since then became a subject of intensive study. It is one of the most well studied peptide hormones (4). Nevertheless, in spite of an enormous amount of research that was already conducted on gastrin, it might be just a beginning of an exciting story. New findings suggest that gastrin has many more important functions than had been recognized in the past, and that it has additional, until recently, unknown cellular and molecular targets that yet need to be characterized. Gastrin is produced mainly by G-cells of antral mucosa and duodenum (5). Low levels of gastrin expression were detected in the pancreas of adult mammals (high in fetal and neonatal rats), in anterior and intermediate pituitary lobes, human spermatogenic cells, bronchial mucosa, vagal neurons, hypothalamo-hypophyseal neurons, and some endocrine cells of the small intestine (6). Gastrin is synthesized in a form of a 101 amino acid residues precursor (7). The major forms of gastrin in circulation are the heptadecapeptide (G-17) and the tetratriaconpeptide (G-34) (8). They are formed from the precursor as a result of removal of the signal peptide, C- and N-terminal extensions and processing of glycine extended intermediates to amidated forms of the hormone (9). Gastrin in mature form shares the same carboxiamidated C-terminus, -Trp-Met-Asp-Phe-NH₂ with cholecystokinin (CCK), which is expressed predominantly in duodenal and jejunal mucosa and in the cerebral cortex. This sequence constitutes the active site of both hormones and is highly preserved during evolution (10). Gastrin and CCK have many overlapping activities, because their structures are similar. Though a major role of gastrin is still considered to be in the stimulation of gastric secretion, recent data suggest that the hormone is indeed multifunctional. It was shown to
increase blood flow through the stomach mucosa (11), it is involved in contraction of the stomach muscle (12), it has trophic effects on gastric and duodenal mucosa and the pancreas (13–18), it stimulates fractional sodium excretion in kidneys, and increases renal plasma flow (19), and may play a role in regulation of pancreatic secretion (20).

The gastrin receptor, which has been cloned and characterized, is the CCK-B receptor (21–26). It binds gastrin and CCK with almost equal affinities. A number of more recent reports suggest that gastrin has a receptor or receptors different from cloned CCK-B receptor. The goal of this review is to provide an updated and referenced summary of cellular and molecular targets of gastrin with an emphasis on a variety of gastrin activities and their physiological links.

THE RECEPTORS (MOLECULAR TARGETS) FOR THE GASTRIN GENE PRODUCT

So far only one receptor for gastrin, the gastrin/CCK-B receptor, was carefully characterized in terms of primary structure and pharmacological properties (21–26). The receptor belongs to the family of G protein coupled receptors. Related CCK-A receptor is highly selective for CCK (27). Structures of both CCK-A and CCK-B receptors from different species, the pharmacology, and structures of corresponding genes were recently reviewed (28,29), and will not be described in detail here. Wide tissue and cell distribution of CCK-A and CCK-B receptors suggests that they play a pivotal role in CCK and gastrin function and mediate a variety of responses to the hormones in different cell types. There is also an increasing amount of information on existence of molecular targets for the gastrin gene products that are different from the CCK-B and CCK-A receptors. Bold et al. (30) have found that the trophic effect of gastrin in a human colon cancer cell line (LoVo) cannot be abrogated by receptor antagonists for CCK-A or CCK-B. LoVo cells also lack mRNA for either of known CCK receptors. Similar lack of inhibition of trophic effect of gastrin by CCK-A and CCK-B receptor antagonists was observed in a subclone of Swiss 3T3 cells, rodent intestinal cells IEC-6, and the fibroblasts (CA) by Singh et al. (31). The authors have termed the receptor that mediates gastrin effects on the three cell lines “gastrin preferring receptor” because it has much lower affinity toward CCK-8 than toward G-17. It shows similar affinities to minigastrin (G-17) and glycine-extended gastrin. Two types of specific gastrin-binding sites were found in Swiss 3T3 cells with \( K_d = 1 \) nM and 100 nM (31). It remains unclear whether the two types of binding sites are different binding states of the same receptor, or are indeed two different receptor types. Both the amidated gastrin and its glycine-extended precursor cause about a 100% increase in the proliferation rate of the three cell lines at concentrations 1–10 nM. The specificity of the receptor is yet to be characterized. The preliminary data show that it has a much longer recognition sequence than the CCK-B receptor. Removal of four N-terminal amino acid residues of G-17, and even just the N-terminal pyroglutamic acid residue, reduces the trophic effects of the hormone. Crosslinking of radiolabeled G-17 bound to Swiss 3T3 cells resulted in modification of a protein with molecular mass of 45 kDa (31).

A different receptor for gastrin, named the gastrin/CCK-C receptor or gastrin-binding protein (GBP) was described in cancer cells by Baldwin (32). The \( K_d \) of the receptor in various gastric carcinomas ranged from 0.2–1.3 \( \mu M \) in the binding of human gastrin, so this receptor has affinity that is three orders of magnitude lower than that of CCK-B or the gastrin-preferring receptor. Cross-linking of the radiolabeled gastrin with the receptor on