Regulation of Gastrointestinal Mucosal Growth

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This article reviews the possible mechanisms initiated by the ingestion and presence of food in the digestive tract that might regulate the growth of gastrointestinal mucosa. Emphasis is placed on direct local nutrition, pancreatic and biliary secretions, and gastrointestinal hormones. The strong and weak points of each of these are discussed in regard to its ability to account for experimental data. Areas of controversy are emphasized and, in some cases, attempts at reconciliation are made. Many of the data in this field of research are descriptive; future studies should focus on the actual mechanisms of regulation.

There are two general types of stimulation that result in growth of gastrointestinal (GI) mucosa. The first of these involves non-GI hormones such as growth hormone [1, 2] and thyroxine [2, 3]. The effects of these hormones and their relationships to GI hormones is the subject of a recent review [4]. The second consists of the factors brought into play by the ingestion and digestion of food. The importance of food was noted, for example, by Steiner et al. [5], who demonstrated that, in rats starved for 6 days, the small intestine lost 53% of its weight while the whole body lost only 32%. They found that the total intestinal cell population decreased, and the RNA, protein, and water content of the individual cells was diminished.

Figure 1 summarizes these mechanisms, showing a breakdown of the factors hypothesized to play a role in the trophic response of GI mucosa to food. These factors will constitute the subject matter of the current review. Three of them, local nutrition, pancreaticobiliary secretions, and GI hormones, are of particular interest and have been intensely investigated during the past 10 years. From the outset I would like to go on record by saying that no single one of these mechanisms can explain all of the experimental observations. The purpose of this review will be to present the strengths and weaknesses of each, to attempt to reconcile areas of difference and controversy, to point out areas where clarification in the form of additional research is needed, and to present a few new concepts for future research.

Definitions

In order to discuss this topic, some agreement must be reached about the meaning of the phrase, "luminal nutrition." Use of this term has been confusing, to say the least. Writing in 1974, Dowling [6] used it to mean nutrition derived from the absorption of foodstuffs by the absorbing cells. In a recent review, Riecken and Menge [7] defined it as "the presence of nutrient material in the intestinal lumen" and state that "this does not imply that the nutrients must be absorbed to exert their effect." This definition is meant to include both direct and indirect effects. They further elaborate that direct effects imply trophic changes brought about by luminal nutrition "in the strict sense of the word." Indirect effects include changes in bacterial flora, hormone release, and secretion. Feldman et al. [8] apparently agree with this definition, but in listing possible mechanisms of intestinal adaptation, they separate luminal nutrition from pancreaticobiliary secretions and hormonal effects. I rest my case as to
the confusion brought about by this term.

Although I do not expect others to follow my example, for the sake of clarity, the term luminal nutrition should be dropped completely and will not be mentioned again in this article. I will use the phrase "local nutrition" to mean the nutritional effect of absorbed digestion products on the absorbing cells. In Fig. 1, this is classified as a direct effect along with increased desquamation brought on, presumably, by the physical effects of food in the GI tract. Indirect effects of food include those produced by released hormones, increased motility and secretion, and increased nervous activity. Hormonal effects are further broken down to include endocrine effects caused by increased levels of hormones in the general circulation and paracrine effects. A paracrine effect is one that is exerted locally on cells in close proximity to the hormone-containing cells. This is a difficult action to prove experimentally, but it is likely that released hormones can affect cells near their sites of release without ever appearing in the general circulation.

It is also important to distinguish between normal growth of intestinal mucosa and adaptive responses. There is no reason to assume that the mechanisms responsible for hyperplasia and hypertrophy of distal intestine following resection of proximal intestine, for example, are identical to those operating under normal physiological conditions. Indeed, they probably are not.

Feeding Studies

Increased food intake results in hypertrophy and hyperplasia of GI mucosa [9]; conversely, fasting or starvation produces mucosal atrophy and hypoplasia [5]. Mechanisms or models used to study the effects of hyperphagia include the diabetic rat, the lactating female rat, and hyperthyroidism. Unfortunately, each of these models also involves changes in circulating levels of non-GI hormones, which make interpretation difficult. Similarly, starvation produces a physiological state resembling that in diabetes, with changes in the levels of a number of hormones.

The GI hormone, gastrin, has been shown to be a trophic substance specific for the mucosa of the oxyntic gland of the stomach [9], small intestine, and large intestine [10]. It also stimulates growth of the exocrine pancreas [11]. Cholecystokinin (CCK), a second gut hormone of duodenal origin, also increases the mass of the exocrine pancreas [12]. Radioimmunoassay has shown that gastrin levels depend on feeding activity. It is assumed that CCK is also released by components of a meal, but due to the lack of a sensitive assay, the levels of this hormone are not known. Increased feeding activity obviously increases the exposure of the mucosa to nutrients, and presumably results in greater secretory activity of the pancreas and liver.

Most feeding experiments have not been designed to separate these mechanisms and, thus, do not provide clues as to which may or may not be responsible for increased mucosal growth. It is also now becoming apparent that gastric levels are affected in all of the various models used. During 3 days of starvation gastrin concentration in rat antral mucosa decreased from 32 µg/g wet weight to 5 µg/g, and serum gastrin levels fell from 330 pg/ml to 70 pg/ml [13]. In these same animals, mucosa from the small intestine exhibited significant decreases in