

Regulation of gastrointestinal secretion: symposium overview

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The term secretion is used to cover a variety of different physiological phenomena, including transport of electrolytes and water across epithelia, release of neurotransmitters by nerve terminals and delivery of proteins to the plasma membrane by exocytosis. All these are relevant to gastrointestinal function, but distinct cellular mechanisms are involved in each case. The primary focus of the symposium on *Regulation of gastrointestinal secretion* was protein secretion by gastrointestinal (GI) cells.

The capacity for protein secretion is found in all eukaryotic cells. It accounts, for example, for the insertion of integral proteins into the plasma membrane as well as for the release from the cell of a variety of different proteins, e.g. extracellular matrix proteins, growth factors, hormones and enzymes. Impressive progress has been made in recent years in characterizing the mechanisms involved in the sequential processes of vesicle budding and fusion that mediate the passage of secretory proteins from endoplasmic reticulum through the Golgi complex and then to the cell surface. There are two separate routes by which protein is passed from the trans Golgi network to the cell surface: the constitutive pathway, which is present in all eukaryotic cells, and the regulated pathway which is characteristic of endocrine and exocrine cells, and neurons. The defining feature of the regulated pathway is the presence of secretory granules that act as storage depots and that are discharged by exocytosis on cell stimulation and specifically on a rise in intracellular Ca. The GI tract and its appendages are certainly the largest concentration of secretory cells exhibiting regulated exocytosis in the body. It is probably also one of the most diverse and functionally heterogeneous collections of such cells.

At the cellular level, the distinction between exocrine and endocrine cells can be defined in terms of cell polarity, and is characterized by the functions of different plasma membrane domains. Thus, in endocrine cells fusion of regulated secretory granules occurs at the basolateral membrane so that secreted material is passed into the interstitial fluid, whereas in exocrine cells exocytosis occurs at the apical membrane and so secreted protein enters the lumen. Entero-pancreatic endocrine cells, like neurons, also seem to possess a second regulated pathway specialized for storage and secretion of small transmitters into the interstitium. In this case, small clear vesicles are generated by a specialized endosomal compartment which, unlike the protein-containing secretory granules, is able to function independently of the Golgi complex.

At the organ level, the control of gastrointestinal secretion has long been recognized to depend on complex interactions between nervous, endocrine, immune and local factors. Collectively these mediate or modulate the effects of stimuli arising in the gut lumen, and so allow overall coordination of GI secretion with the presence of food in the gut. The recurring themes in the present symposium are the identification of luminal stimuli associated with particular physiological functions, the elucidation of neuro-humoral control mechanisms, and characterization of cellular responses at the molecular and genetic level.

The mechanisms regulating secretion of acid in the stomach have been intensively studied over many years and are of considerable importance in that they provide an important target for the drugs used in ulcer therapy. Parsons describes the relevant neuro-humoral control mechanisms and recounts the rationale for the development of histamine H₂ receptor antagonists, and more recently the proton-pump blockers, for inhibition of acid secretion. In addition to their intrinsic clinical importance the histamine H₂ antagonists have also proved to be of decisive importance in resolving long-lasting controversies over the physiological importance of histamine in controlling acid secretion. Moreover, the proton-pump blockers have provided valuable information on the molecular organization and function of the H⁺/K⁺-transporting ATPase (*EC* 3.6.1.36).

The arrival of food in the gut not only triggers the secretion of hormones and neurotransmitters, but also regulates expression of the genes that encode these substances, their biosynthetic enzymes and receptors. Dimaline reviews the evidence for physiological control of gene expression in gastric endocrine cells. The gastric lumen contents, in the form of food or acid, regulate the abundance of mRNA species encoding gastrin, somatostatin, histidine decarboxylase (*EC* 4.1.1.22; HDC; which is the enzyme involved in the synthesis of histamine from histidine) and at least one receptor, the somatostatin SSTR2 receptor. Gastrin is an important mediator of the effect of food on the histamine-producing enterochromaffin-like (ECL) cells, and somatostatin is an important mediator of the effects of gastric acid on gastrin cells. The responses of the ECL cell provide a useful general model: gastrin stimulates histamine release, HDC enzyme activity, the abundance of mRNA species encoding HDC, chromogranin A (which is a protein stored in ECL cell secretory granules) and also VMAT-2 which is the granule membrane transporter thought to be responsible for transport of histamine from cytosol to granule. Over longer periods, gastrin also stimulates ECL cell proliferation. Dimaline explains how the changes in gene expression in ECL cells reveal a graded, integrated and coordinated response to food in the stomach.

The lumen environment of the gut supports a wide variety of potentially-noxious influences, and the long-term health of the GI tract is, therefore, dependent on the existence of matching, or counteracting, defence mechanisms. The mechanisms are complex, but throughout the gut the production of mucus glycoprotein is an important contributor to mucosal protection. Laboisse and co-workers describe the control of mucin secretion by a cell line Cl.16E derived from the human colon carcinoma cell line HT-29. They draw attention to the limitation of studies on cell lines and to the care that is needed in interpreting the physiological significance of findings made in cell lines. However, it is also clear that such studies have been extremely valuable in elucidating possible intracellular control mechanisms, and in generating hypotheses for testing *in vivo*. One advantage of HT-29-derived cells is that they can be grown as monolayers when they assume a polarized phenotype: mucin secretion occurs at the apical membrane in response to stimulation by neuro-endocrine mediators such as acetylcholine, vaso-active intestinal peptide and neurotensin acting at the basolateral membrane. At the apical membrane ATP evokes secretion, although the functional significance of this is still uncertain. Interestingly, a variety of toxins including cholera toxin, and toxin A from *Clostridium difficile* are also stimulants.

The presence of nutrient in the gut provides a stimulus to mucosal growth, and so-called intestinal adaptation has been recognized for many years. Raul & Schleiffer

discuss the mechanisms that account for changes in small intestinal function during maturation and that underlie the transition at weaning from a mucosa adapted to digestion of milk to one adapted to an adult diet. They also discuss the changes in gene expression that occur in mature rat intestine and account for adaptation to different types of adult diet. These mechanisms are interesting in a clinical context and should be considered in the development of specialized nutritional strategies. For example, the maintenance of a healthy intestinal mucosa needs to be kept in mind during total parenteral nutrition since this is crucial for the protection against bacterial translocation which at its most extreme leads to multiple organ failure.

In general, the specific chemical and cellular signals by which lumen nutrients influence GI function are not well understood, and the cellular transduction mechanisms are almost completely unexplored. The control of intestinal hormone secretion by different nutrients, however, has been the subject of study for many years. Knapper and co-workers describe the control of secretion of two intestinal hormones, glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide (GLP)-1(7-36)amide. Both are released by carbohydrate and fat, and both act on the endocrine pancreas. One of the interesting recent developments in this area has been the emergence of evidence that GIP and GLP-1(7-36)amide have additional effects outside the GI tract and pancreas. In particular, they act on adipocytes regulating fat deposition. The full characterization of the functional significance of these effects is now needed.

GI secretions are regulated by a wide range of mechanisms involving not just cells within the GI tract, but others more distant, including the central nervous system. The interaction between nervous and other control systems is complex. Two aspects that are now attracting considerable attention are mentioned by Rozé. First, it is now clear that primary GI afferent neurons, particularly spinal afferents, contain peptides, notably calcitonin-gene-related peptide and substance P, which are released not just at central terminals but also at peripheral terminals where they are thought to mediate responses of the axon-reflex type. Second, afferent neurons may themselves be targets for the action of gut hormones, of which cholecystokinin is probably the best worked example.

Up to about 1980 our understanding of GI secretory mechanisms was based on studies of relatively-acute, or rapidly-acting mechanisms. The elucidation of events at the cellular level that are responsible for rapid secretory responses, for example transient and local changes in intracellular Ca^{2+} , continues to be an active and productive area. However, as the contributions to the present symposium show, it is also necessary to define secretory cell function in terms that extend beyond milliseconds, and take account of changes in gene expression and in tissue growth and differentiation. Future progress will depend on the capacity to explain at the level of the whole organism, the changes that can now be defined in gene expression, cellular and molecular function. The means to work towards this objective are now available.