Teaching the role of secretin in the regulation of gastric acid secretion using a classic paper by Johnson and Grossman

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Walton KL. Teaching the role of secretin in the regulation of gastric acid secretion using a classic paper by Johnson and Grossman. Adv Physiol Educ 33: 165–168, 2009; doi:10.1152/advan.00023.2009.—The regulation of gastric acid secretion has been the subject of investigation for over a century. Inhibition of gastrin-induced acid secretion by the intestine-derived hormone secretin provides a classic physiological example of negative feedback in the gastrointestinal tract. A classic paper by Leonard R. Johnson and Morton I. Grossman clearly shows the ability of secretin to negatively regulate gastric acid secretion, providing students with an example of this feedback loop. In addition, this article demonstrates the step forward in gastrointestinal endocrinology that occurred when pure preparations of secretin and other gastrointestinal hormones first became available. The comparison of the effects of exogenous, purified secretin to the physiological stimulus of acid in the duodenum is an important example of how newly available reagents allow scientists such as Johnson and Grossman to clarify the mechanisms behind previously established processes. One or more figures from this classic paper can be used to give students insight into the role of secretin in the regulation of the function of the gastrointestinal tract and will also give students a clear example of how the careful experimentation and clear interest in gastrointestinal physiology led Johnson and Grossman to advance the field.

FOR OVER 100 YEARS, scientists have investigated the process of digestion and the production of gastric acid. Decades of research support a model of gastric acid secretion that includes three phases: 1) the cephalic phase, in which visual, olfactory, or taste stimuli as well as the very thought of food, trigger gastric acid secretion via parasympathetic activity through the vagus nerve; 2) the gastric phase, in which local enteric as well as vagal reflexes combine with the production of the hormone gastrin to stimulate gastric acid secretion; and 3) the intestinal phase, which is characterized by the production of lower levels of gastric acid. Gastrin acts via the direct stimulation of acid secretion by parietal cells as well as by the stimulation of histamine release by enterochromaffin-like cells (ECL), which provides an additional stimulus of parietal cell activity. As chyme enters the small intestine, gastric acid secretion is inhibited in a negative feedback loop, which is mediated by both nervous reflexes and hormonal controls. Secretin is a hormone produced by S cells in the mucosa of the duodenum and jejunum that plays a major role in neutralizing the acidity of the duodenum. Secretin is primarily associated with promoting the secretion of bicarbonate ions by the exocrine pancreas, but an additional important effect of secretin is to inhibit gastric acid secretion by inhibiting the secretion of gastrin.

These actions of secretin combine to result in the neutralization of the acidic duodenal contents.

Research on the Regulation of Gastric Acid Secretion

Ivan P. Pavlov, the winner of a Nobel Prize for Physiology or Medicine in 1904, was the first to demonstrate that gastric acid secretion was stimulated by the anticipation of a meal, using a surgical procedure in dogs called the Pavlov pouch (for review, see Ref. 10). This preparation involved surgically creating a pouch from the main stomach with a cannula that allowed direct sampling of gastric secretions. The Pavlov pouch was similar to a surgical preparation called a Heidenhain pouch after its inventor, Dr. Rudolf Heidenhain; the primary difference between the Pavlov pouch and the Heidenhain pouch was the maintenance of intact vagal innervation in the former and the lack of vagal innervation in the latter (for reviews, see Refs. 10 and 11). These innovative surgical preparations were used as an experimental model for decades, providing gastrointestinal physiologists with the ability to directly measure gastric acid secretion in live, nonanesthetized dogs.

Dr. Morton Grossman was a prolific, highly respected researcher who published many seminal papers in gastrointestinal physiology; a tribute to Dr. Grossman’s work was recently published by Guth and Kaunitz (7). Dr. Leonard Johnson worked as a postdoctoral fellow with Dr. Grossman, and he continues to publish highly regarded work in gastrointestinal physiology. These two physiologists, both leaders in the field, published together several important and elegant studies to elucidate the mechanisms involved in the regulation of gastric and pancreatic secretions. Their classic paper, titled “Secretin: the enterogastrone released by acid in the duodenum,” represents in a few clear figures the culmination of much work to identify secretin as the agent secreted by the intestinal mucosa that inhibited gastrin-induced gastric acid secretion (9).

Secretin was first identified by Bayliss and Starling in 1902, when they observed that the infusion of acid into a denervated loop of the jejunum resulted in the stimulation of pancreatic secretions (2). They were the first to use the term “hormone” to describe the active chemical agent secreted by the intestinal mucosa. Later researchers determined that a substance released into the blood from the intestinal mucosa, upon contact with acid, inhibited gastric acid secretion (1). The term “enterogastrone” was used to describe intestine-derived inhibitors of gastric secretions (6), and secretin was considered a likely candidate. A series of experiments published by Morton Grossman and others determined that the intravenous injection of secretin purified from extracts of the duodenal mucosa inhibited gastrin-induced acid secretion in Heidenhain pouches (4, 5, 12). However, it remained to be demonstrated that exogenous secretin could account for the same level of inhibition of
gastrin-induced gastric acid secretion as the presence of acid in the duodenum. This paper by Johnson and Grossman (9) compared the effects of a 1-h continuous intravenous infusion of secretin to the effects of an infusion of HCl into the duodenum on gastric secretions to determine whether secretin could indeed account for the same level of inhibition as acid in the duodenum. The ability of exogenous hormone to recapitulate physiological effects is an important criterion in determining whether that hormone has physiological action.

As these experiments were done well before recombinant technology allowed the large-scale production of recombinant hormones, physiologists at this time relied on purified hormone extracts made from tissues and glands or on newly available synthetic hormones. This paper by Johnson and Grossman used commercially available pure secretin given by a 1-h continuous intravenous infusion, which approximated the physiological production of secretin in response to acidification of the intestinal contents. This classic paper is useful for reinforcing the concept of hormonal control of gastric acid secretion. It is also an excellent demonstration for students of how gastrointestinal physiologists determined whether specific hormones were involved in physiological responses. Students should have some introductory background in gastrointestinal physiology and gastric acid production before this activity, either through assigned reading or through previous lectures and discussions. For a short in-class or out of class activity appropriate for undergraduates, Fig. 2 from this article and the associated questions can be distributed to your students. For a 30- to 45-min in-class activity, the instructor may wish to introduce the historical context, general background, and experimental design for Fig. 2 with a brief (10 min) lecture. Students can then work in groups of two to four students to answer the discovery learning questions for an additional 10–20 min. The groups can then reconvene for a 10- to 15-min class discussion of the data and questions.

For a longer, more in-depth study for undergraduates or beginning graduate students, the entire paper can be assigned together with the associated questions. In this model, I suggest providing the full paper and questions to students to be read and completed outside of class. The questions can be turned in as an independent assignment; alternatively, students can work in groups for 10–20 min to discuss their prepared answers at the beginning of the next class session. This can be followed by handing in the assignment or by class discussion of the data and questions, depending on the instructor’s preferences and the amount of time available. I have successfully used Fig. 2 and the associated questions as an out of class, independent assignment in a one-semester anatomy and physiology course for prenursing students with relatively little previous background in reading primary literature, and I believe that the full paper could readily be adapted for use in different courses depending on students’ backgrounds.

Figures for Discovery Learning

Figure 1 from this article can be used to illustrate for students the Heidenhain pouch surgical procedure that allowed Johnson and Grossman to both measure gastric acid secretion and infuse saline or acid into the duodenum in dogs. This preparation is a classical experimental model that allowed the in vivo detection of the physiological control of the gastric acid secretory response. An important point is that the Heidenhain pouch, in contrast to the Pavlov pouch, does not preserve the vagal innervation to the stomach pouch; this allows the effects of hormones to be studied in isolation of nervous reflexes to the tissue.

Figure 2 of this article illustrates the major finding of the classic paper: that the infusion of secretin caused a near-complete inhibition of gastric acid secretion that was similar in magnitude and kinetics to the inhibition produced by instillation of acid into the duodenum. Basal secretions were collected at the beginning of each experiment. After 1 h of basal conditions, purified gastrin was infused intravenously, and an increased production of acid was rapidly observed (as shown by an increase in H⁺ concentration). In control experiments, saline was continuously infused into the duodenum, and the acidity of secretions in the Heidenhain pouch was maintained at a relatively constant pH. However, when pure secretin was administered intravenously over a 1-h period, gastrin-induced acid secretion was rapidly and dramatically reduced. In an important physiological comparison experiment, the infusion of acid at a physiological concentration through the duodenal cannula also resulted in a rapid inhibition of acidity of the Heidenhain pouch secretions, although the magnitude and duration of the maximal response to acid was slightly less than the response to exogenous secretin. This dose of gastrin had previously been demonstrated to be submaximal; the authors also show data from a similar series of experiments using near-maximal doses of gastrin stimulation (Fig. 3 in the original paper, not shown). Similar results were seen in these experimental conditions, further supporting the hypothesis that secretin was the primary mediator of the effects of intestinal acidification on gastrin-induced gastric acid secretion.

The final figure in the current article is Fig. 3 (Fig. 4 in the original paper). This series of experiments was similar to those shown in Fig. 2 but used histamine rather than gastrin to stimulate gastric acid secretion. Consistent with prior work (4, 5), histamine caused an increase in gastric acid production, but neither acid in the duodenum nor intravenous secretin altered histamine-induced acid secretion. This serves as an additional demonstration that exogenous purified secretin had effects consistent with the physiological effects of acid in the duodenum. Later studies have reported that secretin decreases gastrin release (8), with effects on gastrin and gastric acid output mediated at least in part by the stimulation of somatostatin and prostaglandin release (3, 8).
Student Learning Outcomes

After completing this activity, students will be able to:
1. Explain the role of secretin and other factors in the regulation of gastric acid secretion and in the process of digestion.
2. Critically analyze experimental data in gastrointestinal physiology.
3. Discuss appropriate experimental design to investigate the effects of hormones on gastric acid secretion.

Questions for Discovery Learning

Question 1. Describe the cephalic, gastric, and intestinal phases of gastric secretion.

Question 2. Figure 1 shows the Heidenhain pouch model system used in this paper. A similar model system called the Pavlov pouch differs in that the Pavlov pouch model retains innervation by the vagus, but the Heidenhain pouch does not. Propose an experimental question about gastric acid secretion that would be best addressed using 1) a Pavlov pouch and 2) a Heidenhain pouch.

Question 3. What physiological event is mimicked by the infusion of acid (HCl) into the duodenum, as represented by the “HCl” line in the graph shown in Fig. 2? What is the purpose of including this experimental group?

Question 4. Briefly describe the effects of each of the following on gastric acid secretion based on the data shown in Fig. 2:
A. Intravenous administration of gastrin.
B. Intravenous administration of secretin in the presence of intravenous histamine.
C. Addition of acid to the duodenum in the presence of intravenous histamine.

Question 5. How does the effect of secretin compare with the effect of acid in the duodenum? Does this support the conclusion that the effects of acid in the duodenum on gastric acid secretion are mediated primarily by secretin?

Question 6. Explain the other effects of secretin on the gastrointestinal tract and how the effects of secretin combine to regulate digestion.

Questions 7–9 can be included if the entire paper is assigned.

Question 7. Briefly describe the effects of each of the following on gastric acid secretion based on the data shown in Fig. 3 (Fig. 4 in the original paper):
A. Intravenous infusion of histamine.
B. Intravenous administration of secretin in the presence of intravenous histamine.
C. Addition of acid to the duodenum in the presence of intravenous histamine.

Question 8. Based on the data presented in the paper as a whole, predict a mechanism through which secretin may regulate gastric acid secretion.

Question 9. Techniques available for the investigation of hormonal control of gastric acid secretion and other physiological parameters have advanced significantly in the 40 years since this study was published. Design an experiment using modern techniques to further investigate the role of secretin in the regulation of gastric acid secretion. Suggested techniques include (but are not limited to) the use of transgenic and/or knockout animal models, analysis of RNA or protein localization or expression levels, and the use of receptor agonists and antagonists or blocking antibodies.

Teaching Points

Teaching point 1. Both nervous reflexes and hormonal controls contribute to the regulation of gastric acid secretion. The relative importance of vagus input versus hormonal and chemical messengers was the subject of debate for decades, beginning with Pavlov. The use of the Heidenhain pouch (shown in Fig. 1), in which the vagus innervation is not preserved, allowed researchers to investigate gastric acid regulation in the absence of higher nervous system regulation. Although this does not allow direct study of the interplay between neural and hormonal controls, it provides an experimental model that allowed researchers to determine that hormones were important players in gastrointestinal physiology.

Teaching point 2. The inclusion of appropriate controls is vital to clearly demonstrating whether exogenous hormones can recapitulate physiological responses. The negative control in these experiments was the infusion of saline into the duo-
denum of gastrin-stimulated dogs. Gastrin (or histamine) was able to induce marked secretion of gastric acid (HCl) (Figs. 2 and 3). The infusion of acid into the duodenum is a critical physiological control, as it represents the transit of acidic chyme from the stomach to the duodenum. The ability of exogenous secretin to have as strong an effect as the physiological stimulus of acid in the duodenum is a crucial piece of evidence supporting the physiological role of secretin in the regulation of gastric acid secretion.

_Teaching point 3._ In addition, the demonstration that acidification of the intestinal luminal contents triggers mechanisms that decrease gastric acid output provides a good example of negative feedback loops in the gastrointestinal tract. As acidified chyme moves from the stomach into the duodenum, the intestine signals back to the stomach to decrease the production of acid and slow the digestive process. This allows time for further digestion to occur in the intestine, as well as absorption of nutrients, before a new bolus of chyme enters from the stomach.

_Teaching point 4._ Secretin was first identified as and is still primarily considered to be an intestine-derived stimulator of pancreatic secretion. This stimulation of bicarbonate ion secretion from the pancreas has the functional consequence of neutralizing the pH of the intestinal contents. Although it can be challenging for beginning students of endocrinology and physiology to appreciate that hormones can stimulate one effector yet inhibit another, the concomitant stimulation of pancreatic secretions and inhibition of gastric acid production both act to bring the pH of the duodenal contents to a more neutral value.

**Conclusions**

This classic paper by Johnson and Grossman provides a clear picture of the role of gastrin and secretin in the regulation of gastric acid secretion and also gives students an opportunity to engage in the process of science and careful experimentation. The experiments presented do not require students to have an extensive understanding of experimental techniques, as the readout for all the data figures is simply acid production by a surgically created pouch of the stomach. The regulation of gastric acid secretion by parietal cells is complex and involves an interplay between multiple factors, including gastrin, histamine, and acetylcholine. More recent journal articles or textbook readings will allow a more in-depth discussion of the cellular mechanism of gastric acid secretion as a followup to this activity, if desired. However, this paper from 1968, which includes in its references articles from the 1920s, will give student a glimpse of the experiments over the past century that have led to our current understanding of the physiology of gastric secretion.

**REFERENCES**