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This Week's Citation Classic

Gibbs J, Young R C & Smith G P. Cholecystokinin decreases food intake in rats. *J. Comp. Physiot. Psychol.* **84**:488-95, 1973.
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Intraperitoneal administration of the synthetic octapeptide of cholecystokinin, but not of secretin, produced rapid, large, dose-related, transient, and behaviorally specific inhibitions of solid and liquid food intake at test meals in rats without evidence of side effects or illness. Cholecystokinin may play an inhibitory role in the short-term control of feeding behavior. [The *SCI*® indicates that this paper has been cited in more than 560 publications.]

Gut Hormones and Satiation J.

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We were stuck. We had just completed an experiment that provided strong evidence against the hypothesis that decreased glucose utilization was a physiological signal for the initiation of eating under normal circumstances.[1] We had no idea where to look or what to look for as an alternative mechanism for hunger. On the other hand, we were impressed by the simple fact that our monkeys and rats always stopped eating within 15 to 30 minutes after they began. Although we were just as ignorant about the mechanisms that terminate eating as we were about those that initiate eating, we decided that the investigation of the termination of eating was a more accessible problem than hunger because ingested food was clearly the adequate stimulus, and the site of this satiating action of food must be along the path that food took from the mouth, through the stomach, and into the small intestine where digestion was completed and absorption occurred. One of us (GPS) had worked in gastrointestinal physiology during the previous decade and thought that knowledge of the neuroendocrine control of gut function might be a heuristic context for the search for satiety signals from the gut.

We decided to test the effect of gut hormones on food intake for three reasons: First, a number of hormones were released by the mechanical and chemical stimuli of ingested food contacting the luminal surface of the stomach and small intestine. Furthermore, the hormones could act as satiety signals because they were released before eating stopped. Second, a number of the hormones were available in pure or partially pure form and there was considerable knowledge concerning their structure-activity relationships. Third, experiments with administration of hormones were much easier to design and do than experiments concerned with monitoring visceral afferent neural activity during ingestion.

We began with impure preparations of cholecystokinin and secretin because we had been using them in recent experiments concerned with the control of insulin release during food intake elicited by 2-deoxy-D-glucose.[2] The first series of experiments worked. Cholecystokinin inhibited food intake, but secretin did not.

We believe that this paper is cited frequently for three reasons: (1) It was the first report of a significant inhibition of food intake with a synthetically pure gut peptide, the COOH-terminal octapeptide of cholecystokinin, CCK-8; (2) it showed how the interpretation of this effect required experiments designed to eliminate the possibility that the inhibition was due to toxic effects or to interference with the oral movements required for eating; and (3) it proposed five criteria that had to be satisfied before the inhibition of food intake by administration of a hormone could be considered a physiological function of the endogenous hormone.

Much of the work of the past 20 years on the satiating effect of cholecystokinin and other gut hormones has been pursued within the context of the types of experiments and criteria presented in our paper. Demonstrating the physiological function of cholecystokinin proved more arduous than we imagined when we wrote this paper. It depended on the development of specific and potent antagonists, and it was only a year ago that we judged the evidence to be sufficient to conclude that the satiating effect of endogenous cholecystokinin was proven.[3]

Gibbs and Smith remained at Cornell and have been constant collaborators during the past 20 years on the investigation of cholecystokinin and bombesin-like peptides in the control of meal size in the rat. Young won a prize for original research from Cornell University Medical College for his contribution to this work. After a psychiatric residency at Washington University in St. Louis, he returned to Cornell and is now an associate professor of psychiatry doing research on mood disorders in the elderly.

1. **Smith G P, Gibbs J. Strohmayer A J & Stokes P E.** Threshold doses of 2-deoxy-D-glucose for hyperglycemia and feeding in rats and monkeys. ***Amer.** J. Physiol.* 222:77-81. 1972.
2. **Smith G P *&* Root** A **W.** Effect of feeding on hormonal responses to 2-deoxy-D-glucose in conscious monkeys. *Endocrinology* 85:963-6, 1969.
3. **Smith G P & Gibbs J.** The development and proof of the cholecystokinin hypothesis of satiety. (Dourish C T. Cooper S J. Iversen S D & Iversen L L. eds. J *Multiple cholec\stokinin receptors in the CNS.* Oxford. England: Oxford University Press. 1992. p. 166-82.
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