Serotonin-3 receptors in gastric mechanisms of cholecystokinin-induced satiety

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Our understanding of the controls of food intake has increased substantially during the last 30 years. Important in this has been the recognition of the meal as a controlled, physiologically relevant unit of energy intake. During a meal, ingested nutrients accumulate in the stomach, and gradually pass to the small intestine. The gastrointestinal presence of nutrients stimulates the release of peptides and neurotransmitters that coordinate gastrointestinal secretion and motility to facilitate digestion. These events can individually, and in concert, produce signals to the brain that lead to meal termination or satiety (28), and thus determine individual meal size. The gut-brain peptide cholecystokinin (CCK) and the monoamine serotonin (5-HT) are two long-recognized agents of satiation. In this issue of the *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology*, Hayes et al. (16) present important new information about how CCK and 5-HT systems interact to promote peripheral mechanisms of satiety.

Since the original demonstration (14) that systemic administration of CCK inhibits food intake in rats by reducing meal size and duration, CCK has become the best-characterized satiety factor (24). CCK is released from enteroendocrine cells in the proximal small intestine in response to fat and protein. CCK binds to CCK-1 receptors (also known as CCK-A receptors) to promote meal termination (2). CCK activates CCK-1 receptors on mechanoreceptive vagal afferents from the stomach and duodenum, as well as duodenal chemoreceptive vagal afferents, to directly transmit meal-related feedback signals to the brain (29). CCK also activates CCK-1 receptors in the circular muscle layer of the pylorus, causing it to contract. This slows gastric emptying, resulting in gastric distension and the indirect activation of gastric mechanoreceptive vagal afferents (29).
The monoamine serotonin (5-HT) is produced by platelets, endothelial cells, mast cells, serotonergic neurons, and enterochromaffin cells (13). Its wide distribution in the gastrointestinal tract and vasculature have made 5-HT a strong candidate for involvement in peripheral mechanisms of satiety. Parenteral administration of 5-HT reduces food intake by reducing meal size and duration (11). Like CCK, 5-HT is released from intestinal enteroendocrine cells in response to nutrients (21). In addition, 5-HT is also released in response to gastric distension (22). Gastrointestinal release of 5-HT, like CCK, activates vagal afferent fibers (22, 27).

Given the complex pharmacology of 5-HT receptor subtypes, and the emphasis on central 5-HT in feeding (5, 6), the identification of roles for specific 5-HT receptors in peripheral mechanisms of feeding control has been challenging. The 5-HT-3 receptor was long discounted from having an important role in the control of food intake. Systemic administration of antagonists at 5-HT-3 receptors usually produced negative results, and occasionally decreased food intake (7, 23, 30, 32). For some time, the only consistent data for an anorectic role for peripheral 5-HT-3 receptors came from experimentation in an aminoprivic model, in which systemic administration of the relatively selective 5-HT-3 receptor antagonist tropisetron attenuated anorectic responses to a dietary imbalance of essential amino acids (1, 15, 20). So, even though 5-HT and CCK had been proposed to interact in satiety (5, 6, 31), the lack of data supporting a role for peripheral 5-HT-3 receptors in satiation did not encourage investigations of potential interactions between 5-HT-3 receptors and the CCK system.

The first evidence that CCK-1 and 5-HT-3 receptors could interact in feeding came seven years ago, again from experiments with dietary amino acid imbalance (1).
Shortly thereafter, Burton-Freeman et al. (4) showed a cooperative interference by devazepide and tropisetron with the satiety meal patterns after intestinal infusion of fat. The broad significance of these findings for satiation on regular diets sparked interest. Daughters et al. (8) later demonstrated that ondansetron, a selective antagonist for 5-HT-3 receptors, attenuated both the satiety and the hindbrain cFos expression evoked by CCK. In the last few years, substantial progress has been made in defining interactions between CCK-1 and 5-HT-3 receptors in gastrointestinal functions. Hayes et al. (16-19) have engaged in a systematic characterization and testing of functional interactions between these receptors in gastrointestinal mechanisms of satiety. They have used a pharmacological approach (17, 19) coupled with surgical methods (16, 18) to identify which gastrointestinal sites and meal-related stimuli are involved.

First, Hayes et al. have demonstrated that CCK and 5-HT can synergistically decrease food intake (17). Coadministration of 5-HT and CCK at doses that produce hypophagia individually reduces rats’ food intake to a greater degree than expected from the sum of individual effects. The supra-additivity is also evident when 5-HT and CCK are coadministered at subthreshold doses, together reducing feeding significantly and beyond the sum of the non-significant effect of each alone. Collectively, the other pharmacological feeding experiments have made a strong case for synergistic cooperativity between CCK-1 and 5-HT-3 receptors. Doses of the CCK-1 receptor antagonist lorglumide and the 5-HT-3 receptor blocker ondansetron that individually did not affect intake of a sucrose solution, together increased sucrose intake above baseline (19). When these treatments were introduced against a satiety-producing background of CCK, ondansetron attenuated CCK-hypophagia, lorglumide reversed it, and the
combination increased feeding above baseline (19). Further, against an anorexigenic background of CCK plus 5-HT, whereas CCK-1 receptor antagonism only partially reversed the hypophagia, and 5-HT-3 receptor blockade had no effect, the combined counter-treatment of lorglumide plus ondansetron completely normalized food intake (17). Hayes et al. have gone on to define the direction of interaction between 5-HT-3 and CCK-1 receptors. Although ondansetron attenuates CCK satiety (18, 19), lorglumide does not interfere with hypophagia produced by 5-HT (17). This suggests an order of events such that the activation of 5-HT-3 receptors is downstream of the CCK-1 receptor in satiety. This is consistent with the finding that lorglumide completely reversed CCK satiety whereas ondansetron partially attenuated it (19).

Hayes et al. have shown previously (18) that post-oropharyngeal negative feedback is required for satiation via CCK-1 and 5-HT-3 receptors. Ondansetron attenuates CCK-induced feeding suppression in rats real-feeding on lab chow, extending previous work using a palatable liquid diet (8). In contrast, ondansetron has no effect whatsoever on CCK satiety in rats with open gastric fistulas and sham-feeding on sucrose solution. This suggests that ingested food must make physiologically meaningful contact with the stomach and/or the intestine in order for 5-HT-3 receptors to be involved in meal termination. The gastric negative feedback signals are almost exclusively due to volumetric distension (25, 26), whereas intestinal signals result from the nutrient and chemical properties of chyme (26, 28).

Hayes et al. have shown previously that ondansetron interferes with CCK’s ability to inhibit gastric emptying of solid, ingested food, and also of nutritive and non-nutritive gastric loads given by oral gavage (18). Therefore, it is very likely that 5-HT-3 receptors
are recruited in response to gastric signals. In this, their latest contribution to the *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology* (16), Hayes et al. test the hypotheses that 5-HT-3 receptor mediation of CCK-1 receptor satiety depends on gastric versus intestinal feedback. Ondansetron had no effect on the ability of intraintestinal sucrose, even with CCK, to suppress sham-feeding. Thus, 5-HT-3 receptors were likely to be involved only if there was volumetric distension of the stomach. Then, in separate experiments, intestinal sources of feedback were eliminated while the gastric source was enhanced: in [1] sham-feeding rats with inflatable gastric balloons, and [2] in real-feeding rats with pyloric cuffs plus gastric preloads of saline. In both of these experiments, ondansetron attenuated suppression of intake if the gastric distension was at a high but still physiological level of 10 cc. Finally, in a real-feeding paradigm, ondansetron attenuated suppression of food intake by CCK, as well as by CCK plus a 5 cc gastric load of saline. Together, these results demonstrate that satiation through CCK-1 and 5-HT-3 receptor cooperation requires gastric, but not intestinal feedback.

There is little doubt that the organized application of classical approaches, demonstrated nicely here by Hayes et al., can continue to elucidate details of the CCK-1-5-HT-3 satiety pathway. As we learn more about this and other mechanisms promoting satiation, the information gained could have important health-related applications. Disruptions of gastrointestinal satiety mechanisms are thought to contribute substantially to obesity (3), and also to eating disorders such as bulimia nervosa (9, 10, 12, 33). While the central nervous system remains a hotbed for research in energy balance, we must also continue to elucidate the peripheral mechanisms of feeding control. This dual approach is
essential to maximizing our options for therapies to counteract dysregulated energy balance.

REFERENCES


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