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 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 type-3 (5-HT3) receptor was long discounted from having an important role in the control of food intake. Systemic administration of antagonists at 5-HT3 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-HT3 receptors came from experimentation in an aminoprivic model in which systemic administration of the relatively selective 5-HT3 receptor antagonist tropisetron attenuated anorectic responses to a dietary imbalance of essential amino acids (1, 15, 20). So, although 5-HT and CCK had been proposed to interact in satiety (5, 6, 31), the lack of data supporting a role for peripheral 5-HT3 receptors in satiety did not encourage investigations of potential interactions between 5-HT3 receptors and the CCK system.

The first evidence that CCK-1 and 5-HT3 receptors could interact in feeding came 7 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-HT3 receptors, attenuated both the satiety and the hindbrain c-Fos expression evoked by CCK. In the last few years, substantial progress has been made in defining interactions between CCK-1 and 5-HT3 receptors in gastrointestinal functions. Hayes and colleagues (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 and Covasa (17) have demonstrated that CCK and 5-HT can synergistically decrease food intake. 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 nonsignificant effect of each alone. Collectively, the other pharmacological feeding experiments have made a strong case for synergistic cooperativity between CCK-1 and 5-HT3 receptors. Doses of the CCK-1 receptor antagonist lorglumide and the 5-HT3 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-HT3 receptor blockade had no effect, the combined

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counterstreatment of lorglumide plus ondansetron completely normalized food intake (17). Hayes et al. have gone on to define the direction of interaction between 5-HT3 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-HT3 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. (18) have shown previously that postoropharyngeal negative feedback is required for satiation via CCK-1 and 5-HT3 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-HT3 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. (18) have shown previously that ondansetron interferes with CCK’s ability to inhibit gastric emptying of solid, ingested food, and also of nutritive and nonnutritive gastric loads given by oral gavage. Therefore, it is very likely that 5-HT3 receptors are recruited in response to gastric signals. In this, their latest contribution to the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Hayes et al. (16) test the hypotheses that 5-HT3 and serotonin receptors mediate cholecystokinin-induced satiation through gastric distension-induced release of 5-HT (17). This suggests an order of events such that the serotonin type-3 receptor antagonist, ondansetron, augments the anorectic effect of n-amphetamine in nondeprived rats. Pharmacol Biochem Behav 45: 589–592, 1993.


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