Increased food intake and CCK receptor antagonists: beyond abdominal vagal afferents

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The identifying biological actions of CCK, stimulation of gall bladder contraction (18) and pancreatic enzyme secretion (15), were first detected in extracts of small intestinal mucosa more than 75 years ago. Subsequently, the peptide responsible for these actions was isolated and characterized by Mutt and Jorpes (22). CCK is secreted by small intestinal enteroendocrine cells in response to dietary fat and protein in the small intestine. In 1973, Gibbs et al. (12) reported a new behavioral activity for CCK. They observed reduced food intake in rats after injections of exogenous CCK and suggested that CCK participates in the process of satiation, a process that results in meal termination. Subsequent findings over the past three decades support this hypothesis (for review, see Ref. 29). Among the more compelling evidence supporting CCK participation in satiation is that meal size can be increased when antagonists of the type 1 CCK receptor (CCK-1r) are administered systemically before the start of a meal (3, 7, 20, 27).

There is abundant evidence that endogenous and exogenous CCK reduces food intake by acting on vagal afferent neurons. Vagal afferents express CCK receptors (5, 21, 28) and are activated by CCK (1, 8, 39). Furthermore, destruction of vagal afferents either surgically (30) or chemically (40) attenuates reduction of food intake by exogenous CCK and by intestinal nutrient infusions (43) that reduce food intake via CCK-1r-independent mechanisms (42). Therefore, the role of enteroendocrine CCK and vagal CCK-1r in satiation might seem secure. Nevertheless, the following observations suggest that the picture of vagal afferents as sole mediator of CCK-induced reduction of food intake may not be so simple. First, evidence has gradually accumulated that brain CCK may participate in control of food intake. CCK is synthesized in neurons at nearly all levels of the neuroaxis (16), and its receptors are expressed in many brain areas, including some that contribute to control of food intake (17). Microinjections of CCK into several brain areas reduce food intake (2, 9, 36), and infusions of CCK receptor antagonists (6, 11) or anti-CCK antisera (10) increase food intake. Gastrointestinal stimulation has even been reported to release CCK from some brain sites, notably the hypothalamus (35, 37, 38). A second set of observations that indirectly challenges the notion that peripheral CCK receptors are the sole site of the peptide's action in controlling food intake is that CCK-1r antagonists increase food intake even when plasma concentrations of CCK are not elevated. For example, CCK-1r antagonists attenuate reduction of food intake by intestinal infusions of nutrients, such as maltose and maltotriose, that do not trigger detectable intestinal secretion of CCK (4). In addition, CCK-1r antagonists increase meal size even when rats consume diets that do not elevate plasma CCK (3). Third, whereas vagal afferents are necessary for reduction of food intake by systemically injected CCK, they are not necessary for the increased food intake associated with administration of CCK-1r antagonists. For example, Reidelberger (26) demonstrated that increased food intake associated with administration of a CCK-1r antagonist, devazepide, is not abolished in vagotomized rats. Likewise, capsaicin-treated rats also increase their food intake after systemic administration of CCK-1r antagonists (31). Collectively, these results support the hypothesis that a nongastrointestinal source of CCK, acting at CCK-1r remote from the abdominal vagal terminals, participates in the control of food intake. The fact that most experiments supporting a role for endogenous CCK in the control of food intake have used CCK-1r antagonists that penetrate the blood-brain barrier (BBB) makes this hypothesis all the more tenable.

None of these summarized results negate the firm conclusion that vagal afferents mediate reduction of food intake by systemic injections of exogenous CCK, which does not seem to cross the BBB (23). Furthermore, the existence of a brain site for CCK-1r action in altering food intake is not mutually exclusive with participation of vagal CCK receptors in control of food intake by CCK. However, knowing the location(s) of CCK receptors that mediate responses after receptor antagonist administration not only is essential to correctly interpret the results of pharmacological experiments, but it is prescriptive for how CCK's participation in control of food intake must be studied in the future. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Reidelberger and colleagues (27a) report results supporting both vagal and nonvagal sites through which peripherally administered CCK-1r antagonists increase food intake. They compared the effects of a CCK-1r antagonist, devazepide, that penetrates the BBB (25) with the effects of one that does not (A-70104; Ref. 41). Intact rats exhibited increased meal size when either antagonist was administered. This finding is similar to the results of Brenner and Ritter (3), who also found that a peptide CCK receptor antagonist, which presumably did not cross the BBB, increased food intake in rats. The inference drawn from both of these experiments is that if an antagonist is excluded from the brain, its effect must be mediated by an action at peripheral receptors. This conclusion assumes a degree of BBB homogeneity, which may not exist. In fact, a number of brain sites where microinjections of CCK or antagonists alter food intake exhibit vascular specializations that allow penetration of large, polar blood-borne molecules (13, 14). However, an additional experiment reported in the present paper by the Reidelberger group addresses this issue by comparing the feeding effect of the BBB-permeant CCK receptor antagonist with that of the impermeant antagonist in vagoto-
mized rats. By this comparison they found that although the BBB-permeant antagonist increased feeding in both vagotomized and intact rats, the antagonist that does not penetrate the BBB increased food intake only in rats with intact vagi and not in vagotomized rats. This latter finding affirms participation of vagal CCK receptors, and presumably peripheral CCK, in increased food intake after CCK-1r antagonism. However, the fact that the response to the BBB-permeant antagonists is insensitive to subdiaphragmatic vagotomy is consistent with the hypothesis that increases in food intake evoked by some systemically administered CCK receptor antagonists cannot be attributed entirely to an action at abdominal CCK receptors.

The location(s) of CCK receptors that are accessible to devazepibe but not to A-70104 cannot be specified from the current results of Reidelberger et al. Although nonvagal CCK-receptive neurons in the brain may be responsible for increased food intake after devazepibe treatment, this interpretation should not be adopted prematurely. The current results do not rule out an action of devazepibe on the surviving components of vagal afferent neurons themselves, either in the hindbrain or in the nodose ganglion. The vagal afferent cell bodies, and presumably their central terminals, survive subdiaphragmatic vagotomy (24), and these surviving afferent components might be differentially accessible to the two CCK receptor antagonists used in this study. This possibility is intriguing and bears on the cellular mechanisms by which CCK receptor antagonists evoke increased food intake. Specifically, the demonstrated ability of CCK receptor antagonists to increase food intake in the absence of increased levels of circulating CCK suggests that neuronal CCK-A receptors may possess a degree of constitutive signaling (19). If this is the case, then CCK-1r antagonists may act as inverse agonists on intact or remnant vagal afferent components, thereby increasing food intake in the absence of detectable CCK agonist.

If devazepibe-induced increases in food intake by vagotomized rats are, in fact, due to the action of the receptor antagonist on neurons in the brain, the results could reflect what seems to be an organizing principle of many neurohumoral interactions. Briefly stated, hormones, neurotransmitters, and perhaps even metabolic substrates tend to act in complementary fashion at multiple sites along neural circuits that control behaviors or physiological responses. A non-CCK-related example of this principle can be drawn from the literature on glucose homeostasis. When brain glucose availability is threatened, epinephrine neurons in the ventral medulla mediate ACTH/corticoesterone secretion via projections to the hypothalamus (33), increased food intake via local hindbrain connections (32), and increased adenomediulary epi-
ephine secretion via descending projections to sympathetic preganglionic neurons in the spinal cord (32). Epinephrine release by nerve terminals in the brain and cord is important for communicating and integrating gluco regulatory responses in several distinct central circuits. However, epinephrine also serves as the peripheral endocrine effector for mobilizing liver glycogen to restore the brain’s glucose supply (34). Thus both central and peripheral epinephrine and epinephrine receptors play crucial and complemental roles in glucoregulation. As with epinephrine and glucose regulation, it may be that CCK of intestinal origin is but one source of CCK that participates in the control of food intake. Likewise, vagal afferent CCK receptors may modulate first-order viscerosensory signals in

the interest of energy homeostasis, whereas CCK released as a central neurotransmitter may participate in the integration of viscerosensory information at other locations along the central neuroaxis to generate an integrated physiological response. Increased food intake being an endpoint could result from antagonism of CCK receptors that evoke different “parts” of the behavioral “whole.”

REFERENCES