Context-dependent transduction of within-meal afferent signaling

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DURING A MEAL, the physical and chemical properties of ingested food evoke a variety of feedback signals that eventually lead to meal termination. Food accumulates in the stomach, resulting in gastric distension, and a significant portion of ingested nutrients passes quickly from the stomach into the intestine, contacting receptive elements sensitive to both the volume and chemical character of the digestion products. Gastrointestinal peptide release is stimulated and neural elements are activated. This afferent cascade eventually results in meal termination. The transduction of any individual feedback signal is poorly understood at best, and we have almost no understanding of how information from all the concurrent signals is integrated and transduced.

In the Covasa et al. (4) article in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, the role of glutamate in mediating the transduction of these signals is explored. Specifically, they look at how blockade of the glutamate NMDA receptor alters the ability of the brain-gut peptide CCK to inhibit feeding. Prior work has shown that systemic or local hindbrain administration of the NMDA receptor antagonists results in increases in meal size in a variety of experimental settings (1, 2) leading to the suggestion that NMDA glutamatergic synapses are important mediators of vagal afferent hindbrain input.

CCK has been shown to play an important role in controlling meal size. CCK is released from intestinal L cells in response to the intraluminal presence of nutrient digestion products (10). Exogenous CCK potently inhibits food intake (6, 7) and a physiological role for endogenous CCK in meal termination has been demonstrated from experiments using CCK receptor antagonists or genetic models deficient in CCK-A receptors. Antagonist administration results in increased meal size and meal duration (11), and rats lacking CCK-A receptors have chronically elevated meal sizes (12). CCK’s ability to bring about meal termination depends on its ability to activate vagal afferent fibers. The satiety actions of CCK are blocked by either surgical (21) or chemical vagotomy (16). CCK has been shown to induce an elevation in glutamate concentration in the nucleus of the solitary tract, the site of vagal afferent terminations, and the NMDA receptor antagonist MK-801 blocked a CCK-induced suppression of sucrose intake (1). Together these data suggest an NMDA receptor mediation of CCK satiety.

The data provided by Covasa et al. (4) demonstrate an interesting and important dissociation. The NMDA antagonist MK-801 blocks the satiety actions of CCK in real-feeding situations but does not affect the ability of CCK to inhibit sham feeding—a paradigm in which intake is significantly elevated due to an open gastric fistula so that ingested nutrients drain from the stomach and do not result in gastric distension or intestinal stimulation. That is, MK-801 apparently blocks the actions of CCK when it is acting as part of a feedback cascade but does not affect its action under conditions when CCK is working alone to inhibit ongoing intake.

This result is important for a number of reasons. First it suggests that CCK may be affecting food intake through multiple mechanisms. There is precedence for this idea. CCK plays a variety of roles in the overall digestive process. It inhibits gastric emptying through gastric relaxation and pyloric contraction (13, 15). It stimulates the release of pancreatic enzymes (9). CCK may be affecting intake through a direct action or may contribute to satiety through actions that are secondary to some of its gastrointestinal effects. For example, CCK-induced inhibition of gastric emptying has been proposed to contribute to CCK satiety (13). Under certain conditions, the efficacy of CCK to inhibit food intake is increased when CCK is given in combination with an intragastric preload (13, 19). It is thought that CCK’s actions in delaying gastric emptying and the resulting gastric distension add to the direct effects of CCK on food intake (14).

More importantly, these results from Covasa et al. (4) suggest that the transduction of a feedback signal may depend on the context in which it occurs. CCK has been shown in the past to activate vagal afferent fibers with both intestinal and gastric terminations. CCK activates intestinal chemoreceptive fibers and intestinal and gastric fibers that are also responsive to distension (17, 18, 20). In these fibers, there is not only direct activation by CCK, but CCK also sensitizes these fibers to intraluminal distension such that less distension is required for the same amount of activation either during activation by CCK or after CCK-induced activation at a time when activity has returned to baseline levels (18). The dissociation of blocking CCK-induced satiety in real but not in sham feeding suggests that an NMDA glutamatergic synapse is critical in transducing a modulatory rather than a direct action of CCK. Because prior work has demonstrated that NMDA receptor blockade fails to affect the inhibition of food intake produced by intestinal nutrient infusions (3), the present findings suggest that MK-801 is blocking an action of CCK in modulating gastric feedback signaling.

There are other examples where the context in which a signal is provided alters its ability to modify food intake. For example, whereas pancreatic glucagon inhibits meal size when administered in a real-feeding situation, it fails to affect sham feeding (5). However, if given in combination with CCK in a sham-feeding paradigm, glucagon will significantly increase the efficacy of CCK’s satiety actions (8). These data suggest that glucagon acts by modulating other within-meal feedback signals. In sham feeding, the signal that glucagon would normally modulate is absent. However, the feedback provided by CCK in this paradigm provides a sufficient substrate for glucagon-induced modulation.

The Covasa et al. (4) data provide important insights into the transduction of satiety signaling. They imply that meal-stimu-
lated afferent feedback is complex and not unitary. They further support the view that significant integration can take place at the level of peripheral afferents. Finding that some feedback controls rely on NMDA glutamatergic synapses, whereas others do not, tells us that vagal afferent signals do not rely on a single neurotransmitter/receptor interaction for communication with hindbrain neurons. Rather, vagal afferent activity induced by different modalities of stimulation likely has qualitatively differing inputs to the hindbrain. Such input diversity would permit hindbrain integration of multiple forms of information arising from the presence and movement of nutrients through the gastrointestinal tract.

REFERENCES