

Focus on Savastano, Hayes and Covasa (9)

**From gut nutrient sensing to nutrient perception: a cooperative role involving
CCK and 5-HT?**

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Running title: From gut nutrient sensing to nutrient perception

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Abstract

Gut-brain axis interplay remains a major question in physiology. The release of 5-HT by endocrine cells was previously demonstrated to respond to different stimuli including pressure sensors and sodium-glucose cotransporter whereas CCK release responds to apolipoprotein A-IV and Pept1 activation. The paper from Savastano, Hayes and Covasa extends the release of 5-HT and 5-HT₃ receptor activation to lipid and shows cooperation between CCK and 5-HT in luminal lipid-related informations. This concept could represent a key mechanism in the understanding of the interplay between gut mechanosensitivity, gut chemosensitivity and specific nutrient sensing, transduction, central encoding and perception. Whether apolipoprotein A-IV or another lipid-associated signal is involved in the transduction mechanism remains to be determined. The central encoding of the 5-HT₃ and CCK₁ receptors vagus-mediated mechanical and chemical-related sensory informations also represents an exciting area for future research.

Understanding the mechanisms involved in gut-brain axis interplay remains a major question in physiology. It is established that intrinsic and extrinsic afferent fibers from nerves of the gastrointestinal tract continuously receive informations related to a number of mechanical and chemical stimuli applied to the mucosa of the small intestine. They transmit these informations to the enteric nervous system (ENS) and to the central nervous system (CNS), respectively. Altogether they exert feedback control of both gastrointestinal muscle contraction and intestinal secretion and also participate to the central feeling of satiation and satiety and to the control of food intake. The paper from Savastano, Hayes and Covasa (9) in this issue of *AJP, Integrative and Comparative Physiology* showing cooperation between CCK and 5-HT in luminal lipid-related informations represents an interesting contribution to the understanding of these complex mechanisms.

The regulatory mechanisms involving mechanosensitivity and chemosensitivity of intrinsic and extrinsic gut afferent fibers are of particular importance since they participate, during meals, to the overall control and concomitant adaptation of food intake, meal digestion, and nutrient assimilation. They adapt food ingestion to stomach distension, regulate intestinal processes according to the entry of nutrients from the stomach, and participate to the regulation of the supply of nutrients and energy to the body. The extent of the gut mechanosensitivity and chemosensitivity has been inferred from *in vivo* physiological experiments in a variety of animal models and in humans. They demonstrated that gastric and intestinal distension triggers the peristaltic reflex, affect gastric secretion, and induce satiation and meal termination. Similarly, luminal perfusion of the intestine with acid, carbohydrate, lipid, protein, amino acids, or high osmolarity solutions is known to decrease gastric motility, delay gastric emptying, decrease gastric acid secretion, induce satiation or satiety and produce an inhibition of food intake. Despite numerous studies conducted over the last decades, many controversies still remain on the transduction mechanisms in the nerve terminals responding to mechanical and chemical stimuli, the precise properties and responses of individual intrinsic and extrinsic afferent neurons, the cooperative processes by which these different and complex signalling pathways transmit specific mechanosensitive and chemosensitive informations to the ENS and CNS, the central encoding of these informations, and the precise mechanisms by which they participate to the regulation of gastrointestinal processes and to the control of food intake.

Although afferent terminals may express specific receptors on the terminal membrane, the transduction mechanism that received considerable attention is the presence of “taste like” cells in the intestinal mucosa. In response to mechanical or chemical luminal stimuli, these cells pass on the information to the ENS and CNS through the release of neuroactive modulators acting on neurons or neuron endings located in their close vicinity. The mucosal sensitive cell candidates are enteroendocrine cells releasing peptide hormones such as 5-HT, cholecystokinin (CCK), secretin, corticotrophin-releasing factor, somatostatin, orexin, or peptide YY in response to luminal nutrients. When administered exogenously several of these peptide hormones mimic the effects of intestinal nutrients on gut motor and secretory function and on food intake. This interaction involving “taste like” cells and neuroactive modulators acting on terminal afferent extends the sensory repertoire of afferent neurons to luminal stimuli that could not be encoded by their direct action on terminals in the lamina propria. Previous studies showed the important role of intestinal 5HT and CCK released from these intestinal enteroendocrine cells. They appear to be mediators in the signalling of many luminal mechanical and chemical stimuli to intrinsic and extrinsic afferent fibers. As for CCK receptors (CCK1), 5-HT receptors have been identified on vagal and spinal afferent neurons and are of the 5-HT₃ receptor subtype.

The specific transduction mechanisms in the nerve terminals responding to the different mechanical and chemical stimuli have been also subjected to different hypotheses. The gastrointestinal mechanosensitivity has been discussed for several decades and different results demonstrated enterochromaffin cells and 5-HT as pressure transducers and neuroactive modulator, respectively (4,5). The results indicated that 5-HT released from enterochromaffin cells in response to pressure stimulated intrinsic afferent neurons within the enteric nervous system leading to activation of the peristaltic reflex. Accordingly, Fos protein expression is increased in primary afferent neurons in the submucosal plexus in response to gut distension and this effect was 5-HT-dependant. It is also established that the presence of nutrients within the intestinal lumen play an essential role in chemosensitivity of mucosal afferents (4,5,8). There is evidence for a physiological role of enteroendocrine cells and of 5-HT and CCK, as luminal chemosensitive transducers and neuroactive modulators, respectively. In addition, specific transduction mechanisms have been demonstrated for the different nutrients. According to

current ideas, activation of terminal afferents by carbohydrate proceeds through the release of 5-HT acting at 5-HT₃ receptors, whereas activation of terminal afferent by protein and lipid proceeds through the release CCK acting at CCK₁ receptors. These subsequent 5-HT and CCK-dependant discharge through receptor activation in intrinsic and extrinsic afferents result in reflex alteration of gastric function and decrease in food intake. Whether in this model specific information for carbohydrate, lipid and protein can be transmitted by individual intrinsic and extrinsic afferent neurons and what is the central encoding of these informations remains unclear.

Interestingly, the paper from Savastano, Hayes and Covasa (9) in this issue as well as a previous paper from the same group (6) strongly supports the hypothesis of cooperation between CCK and 5-HT in these processes. The concept of cooperation between neuroactive modulators including 5-HT and CCK could represent a key mechanism in the understanding of the interplay between gut mechanosensitivity, gut chemosensitivity and specific nutrient sensing, transduction, central encoding and perception. This paper provides evidence that not only CCK and CCK₁ receptors but also 5-HT and 5-HT₃ receptors participate in luminal lipid-induced vagal afferent activation and induction of satiation. Taking these and other results allows postulating that carbohydrate could elicit the release of 5-HT but not CCK, protein could elicit the release of CCK but not 5-HT, and lipid could elicit the release of both CCK and 5-HT. In this model an increase in luminal lipid reinforce 5-HT release through the action of CCK on gut distension and subsequent mechanosensitive induction of 5-HT secretion by enterochromaffin cells. These hypotheses could stimulate further research on the mechanisms involved in the differentiation between nutrients in the information transmitted by vagal afferent fibers to the CNS. These researches include the transduction mechanisms involved in the release of 5-HT and CCK in response to the different nutrients, as well as the central encoding of the subsequent 5-HT₃ and CCK₁ receptor-dependant vagus-mediated informations.

The release of 5-HT by endocrine cells was previously demonstrated to respond to different stimuli including pressure sensors and sodium-glucose cotransporter (2) whereas CCK release responds to apolipoprotein A-IV and Pept1 activation (1,3). As a consequence, the physiological stimuli for the release of 5-HT from enteroendocrine cells may be both chemical and mechanical. The paper from Savastano, Hayes and Covasa (9) extends the release of 5-HT and 5-HT₃

receptor activation to lipid but whether apolipoprotein A-IV or another lipid-associated signal is involved in the transduction mechanism remains to be determined. The central encoding of the 5-HT₃ and CCK1 receptors vagus-mediated mechanical and chemical-related sensory informations also represents an exciting area for future research. Vagal pathways convey the sensory informations to the brainstem. Vagal cell bodies lie in the nodose ganglia and project centrally to the nucleus tractus solitarius in the brainstem from where information is processed and relayed to higher brains areas (10). Whether and how different combinations of CCK1 and 5-HT₃ vagal afferent fibers receptors activation are differently traduced and encoded in the CNS remains to be further evaluated. The threshold for activation of sensory neurones is not fixed but can be modulated by a number of different mediators and the cooperation between CCK and 5-HT could be involved in the plasticity of the response. In addition some results suggests that 5-HT and CCK act on distinct subpopulations of vagal mucosal afferent nerves and a differential activation of these different subpopulations would result in differential encoding of the response in the nucleus tractus solitarius (7).

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