

## Luminal Influences to Orchestrate Gastroenterological Hormone Secretion: The Fat, Long-Chain Fatty Acid, Cholecystokinin, Glucagon-Like Peptide 1 Axis

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The paper by Beglinger *et al.* (1) in this issue of the *Journal* elegantly demonstrates that fat-induced glucagon-like peptide 1 (GLP-1) secretion is mediated by hydrolysis of triglycerides to long-chain fatty acids (FAs) that then activate cholecystokinin (CCK) release, which in turn stimulates GLP-1 release through the CCK receptor.

The study design was in normal young men who swallowed a feeding tube that was inserted through the nose, with the distal end of the tube positioned in the duodenum.

In the first experiment, a 2-h infusion of control or olive oil was administered intraduodenally. The latter was infused either alone or together with lipase inhibitor orlistat (tetrahydrolipstatin). In this experiment, triglycerides in the form of olive oil induced a robust increase in plasma GLP-1 and CCK levels, which were prevented by coinfusion of orlistat.

The second experiment was performed with a similar design, except that the effects of free fatty acids (FAs) sodium caprylate (C8:0) or sodium oleate (C18:1) and placebo infusion were examined. Oleate infusion induced a similar increase in plasma GLP-1 and CCK to that observed with olive oil in the first experiment. However, caprylate was ineffective in increasing either GLP-1 or CCK.

This result is consistent with previous studies showing that saturated FAs with chain lengths of 4, 10, or 11 were ineffective in stimulating CCK release, whereas those of 12, 14, or 18 carbons were active and equally effective (2). Interestingly, this chain length dependence corresponds with the physical properties of the FAs because C11 and shorter are liquid at body temperature,

whereas C12 and longer chains are solids that require emulsification by bile salts for their digestion. This is further complicated by the observation that some polyunsaturated FAs can stimulate CCK and GLP-1 less effectively and with slower kinetics than saturated FAs (3).

The third experiment consisted of sodium oleate with or without iv dexloxiglumide (DEXLOX), a CCK antagonist. Intravenous DEXLOX largely abolished the increase in plasma GLP-1 and amplified the increase in plasma CCK in response to intraduodenal oleate.

This paper is important in that it presents an integrative biological model of the regulation of GLP-1 by luminal nutrients. Ingested FAs, amino acids, or glucose are each potent stimuli for GLP-1 release, but these nutrients do not have this effect when given intravenously (4). Other monosaccharides such as fructose and galactose also stimulate GLP-1 release, but less effectively than glucose (4, 5).

The authors propose that after lipid ingestion, fat hydrolysis in the proximal intestine plays a crucial role in regulating digestive processes. Adequate fat hydrolysis initiates the process through the release of long-chain FAs that stimulate CCK, which then orchestrates a number of digestive functions including the stimulation of GLP-1.

GLP-1 regulation by glucose and by long-chain FAs provide examples of different mechanisms of luminal actions. The time course of oral glucose-stimulated GLP-1 is more rapid and shorter lived (4), and studies of isolated tissues and cell lines suggest that the GLP-1-producing L cells can directly respond to glucose (6). Thus, we see a fast response

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Abbreviations: CCK, Cholecystokinin; FA, fatty acid; GLP-1, glucagon-like peptide 1.

when the proximal L cells “taste” glucose, whereas the effects of lipid are stronger and slower in onset, last longer, and thus are likely to involve all L cells in the small intestine through hormonal regulation by CCK.

Beyond the CCK, GLP-1 axis, luminal actions need to be considered in the regulation of other gastrointestinal hormones as well. For example, dietary medium-chain FAs are used directly in the acylation of ghrelin, affecting both ghrelin secretion and the length of its acyl side chain (7, 8). Furthermore, the mechanism(s) involved in the effectiveness of gastrointestinal bypass surgery and the sleeve procedures for weight loss and control of diabetes mellitus likely involve the disruption of this important luminal enteral communication (9, 10). This study exemplifies the use of human clinical investigation to help unravel the complexity of the largest endocrine organ in the body, the gastrointestinal tract; it is as challenging as understanding brain function.

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