L-cell physiology and glucagon-like peptide-1 (GLP-1) secretion

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The incretin hormone Glucagon-like peptide-1 (GLP-1) is secreted post-prandially from intestinal L-cells. GLP-1 mimetics and inhibitors of dipeptidy-peptidase-4, which prolong the plasma half-life of GLP-1, are now widely used in the treatment of diabetes to boost insulin secretion. GLP-1 and peptideYY, which is co-secreted from L-cells, also have anorexic effects and postprandial plasma increases of both peptides are significantly elevated within days after Roux-en-Y gastric bypass surgery. While this demonstrates the existence of reserve peptide pools that might be recruited therapeutically by stimulating L-cells, the mechanisms underlying L-cell secretion have been difficult to characterise, partly due to the scattered location of L-cells in the epithelium with little distinguishing characteristics to surrounding enterocytes at light microscopy magnification. Our lab created transgenic mice fluorescently tagging GLP-1 expressing cells and showed that they are, similar to endocrine cells in the pancreas, electrically excitable and that glucose increases action potential firing rates and cytosolic calcium concentrations. In contrast to pancreatic beta cells, that sense glucose downstream of increased metabolism and rises in cytosolic ATP, L-cells deploy apically located sodium-coupled glucose transporters (SGLT-1). This is evidenced by the fact that L-cells respond to non-metabolisable glucose analogues like alpha-methyl-glucose pyranoside (aMDG), that glucose triggered GLP-1 secretion can be blocked by the SGLT-1 inhibitor phloridzin and is absent in cultures from SGLT-1 knock-out mice. In the last decade we have identified a number of L-cell expressed receptors involved in sensing luminal constituents. One of these is the bile-acid receptor GPBAR1, a predominantly Gs coupled receptor, stimulation of which results in GLP-1 release from mixed primary intestinal epithelial cultures. Using Ussing-chambers, which allow application of drugs from either the apical or basolateral side of the intestinal epithelium, we observed that apically applied bile acids failed to stimulate GLP-1 secretion when sodium coupled bile acid transport was blocked pharmacologically. Although this appeared to be reminiscent of the role of SGLT-1 in glucose sensing, the role of bile acid transport is different; bile acids stimulated strongly when applied basolaterally, which was absent in GPBAR1 knock-out derived tissue and inhibition of sodium coupled bile acid transport had no significant effect on GLP-1 secretion from mixed epithelial cultures in which the distinction between apical and basolateral access is lost. In conclusion, while glucose is sensed through direct transport into L-cells from the luminal side, explaining why incretin secreting cells are blind to elevation of plasma glucose, bile acids need to be absorbed to reach their basolaterally located G-protein coupled receptors. In the ileum, the main site of bile acid reabsorption, the basolateral signal might be dominated by the availability of luminal bile, but in other intestinal segments, where GPBAR1 is also expressed on L-cells, this might allow the integration of bile acid plasma pools with local stimulatory signals within the L-cell.