Dokumenttyp: journal article

Autor(en) des Beitrags: Lauffer, LM; Iakoubov, R; Brubaker, PL

Titel des Beitrags: GPR119 is essential for oleoylethanolamide-induced glucagon-like peptide-1 secretion from the intestinal enteroendocrine L-cell.

Abstract: OBJECTIVE: Intestinal L-cells secrete the incretin glucagon-like peptide-1 (GLP-1) in response to ingestion of nutrients, especially long-chain fatty acids. The Galphas-coupled receptor GPR119 binds the long-chain fatty acid derivate oleoylethanolamide (OEA), and GPR119 agonists enhance GLP-1 secretion. We therefore hypothesized that OEA stimulates GLP-1 release through a GPR119-dependent mechanism.

RESEARCH DESIGN AND METHODS: Murine (m) GLUTag, human (h) NCI-H716, and primary fetal rat intestinal L-cell models were used for RT-PCR and for cAMP and GLP-1 radioimmunoassay. Anesthetized rats received intravenous or intraileal OEA, and plasma bioactive GLP-1, insulin, and glucose levels were determined by enzyme-linked immunosorbent assay or glucose analyzer. RESULTS: GPR119 messenger RNA was detected in all L-cell models. OEA treatment (10 micromol/l) of mGLUTag cells increased cAMP levels (P< 0.05) and GLP-1 secretion (P< 0.001) in all models, with desensitization of the secretory response at higher concentrations. GLP-1 secretion was further enhanced by prevention of OEA degradation using the fatty acid amide hydrolase inhibitor, URB597 (P< 0.05-0.001 vs. OEA alone), and was abolished by H89-induced inhibition of protein kinase A. OEA-induced cAMP levels and GLP-1 secretion were significantly reduced in
mGLUTag cells transfected with GPR119-specific small interfering RNA (P< 0.05). Application of OEA (10 micromol/l) directly into the rat ileum, but not intravenously, increased plasma bioactive GLP-1 levels in euglycemic animals by 1.5-fold (P< 0.05) and insulin levels by 3.9-fold (P< 0.01) but only in the presence of hyperglycemia. CONCLUSIONS: The results of these studies demonstrate, for the first time, that OEA increases GLP-1 secretion from intestinal L-cells through activation of the novel GPR119 fatty acid derivate receptor in vitro and in vivo.