Novel biological action of the dipeptidylpeptidase-IV inhibitor, sitagliptin, as a glucagon-like peptide-1 secretagogue.

Abstract:

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted into the circulation by the intestinal L cell. The dipeptidylpeptidase-IV (DPP-IV) inhibitor, sitagliptin, prevents GLP-1 degradation and is used in the clinic to treat patients with type 2 diabetes mellitus, leading to improved glycated hemoglobin levels. When the effect of sitagliptin on GLP-1 levels was examined in neonatal streptozotocin rats, a model of type 2 diabetes mellitus, a 4.9 ± 0.9-fold increase in basal and 3.6 ± 0.4-fold increase in oral glucose-stimulated plasma levels of active GLP-1 was observed (P< 0.001), in association with a 1.5 ± 0.1-fold increase in the total number of intestinal L cells (P< 0.01). The direct effects of sitagliptin on GLP-1 secretion and L cell signaling were therefore examined in murine GLUTag (mGLUTag) and human hNCI-H716 intestinal L cells in vitro. Sitagliptin (0.1-2 ?M) increased total GLP-1 secretion by mGLUTag and hNCI-H716 cells (P< 0.01-0.001). However, MK0626 (1-50 ?M), a structurally unrelated inhibitor of DPP-IV, did not affect GLP-1 secretion in either model. Treatment of mGLUTag cells with the GLP-1 receptor agonist, exendin-4, did not modulate GLP-1 release, indicating the absence of feedback effects of GLP-1 on the L cell. Sitagliptin increased cAMP levels (P< 0.01) and ERK1/2 phosphorylation (P< 0.05) in both mGLUTag and hNCI-H716 cells but did not alter either intracellular
calcium or phospho-Akt levels. Pretreatment of mGLUTag cells with protein kinase A (H89 and protein kinase inhibitor) or MAPK kinase-ERK1/2 (PD98059 and U0126) inhibitors prevented sitagliptin-induced GLP-1 secretion (P< 0.05-0.01). These studies demonstrate, for the first time, that sitagliptin exerts direct, DPP-IV-independent effects on intestinal L cells, activating cAMP and ERK1/2 signaling and stimulating total GLP-1 secretion.