

Endocrine/Cardiovascular – GLP-1 Secretion

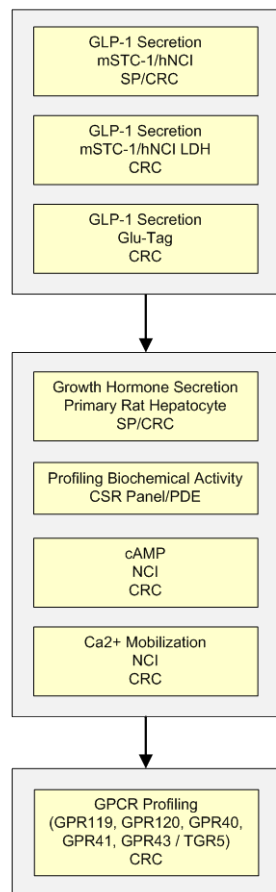
Glucagon-like peptide 1 (GLP-1) is derived from transcription of the proglucagon gene followed by post-translational modifications of proglucagon to the following biologically active peptides: GLP-1 (7-37) and GLP-1 (7-36) NH₂. GLP-1 secretion by ileal L cells is dependent on the presence of nutrients in the lumen of the small intestine. GLP-1 is a potent anti-hyperglycemic hormone inducing glucose-dependent insulin secretion and suppressing glucagon secretion. The glucose dependency of this mechanism is particularly important because GLP-1 does not stimulate insulin secretion and cause hypoglycemia when plasma glucose concentrations are in the normal fasting range.

The GLP-1 secretion, diabetes phenotypic module identifies compounds that stimulate secretion of glucagon-like peptide one (GLP-1) in mouse and human cell lines derived from gastrointestinal tract tissue. GLP-1 secretion is measured using a Lilly proprietary ELISA assay that was specifically designed to detect the appropriate forms of GLP-1 secreted from these cells. If active in the cell-based GLP-1 assay, molecules will be further tested for selectivity in assays that measure activation of GPCRs known to stimulate GLP-1 secretion. Compounds of interest act to stimulate GLP-1 secretion through novel, unknown mechanisms.

- Glucagon-Like Peptide 1-Based Therapies for Type 2 Diabetes: A Focus on Exenatide; Kathleen Dungan and John B. Buse; *Clinical Diabetes*: 29 (1), (Winter 2011).
- Glucagon-Like Peptide 1 Secretion by the L-Cell; Gareth E. Kim and Patricia L. Brubaker; *Diabetes*: 55 (supplement 2), (December, 2006).

Flow Scheme & Assay Measures

Endocrine/Cardiovascular: GLP-1 Secretion



Text

GLP – 1 Secretion

Primary Assays

GLP-1 Secretion mSTC-1 SP / CRC (% Stimulation) / (EC₅₀)
GLP-1 Secretion hNCI CRC (EC₅₀)
Cytotoxicity mSTC-1/hNCI LDH Secretion CRC (EC₅₀)
GLP-1 Secretion Glu-Tag CRC (EC₅₀)

Secondary assays

Growth Hormone Secretion Primary Rat Hepatocyte SP / CRC (% Stimulation / EC₅₀)
Profiling Biochemical Activity - CSR Panel (K_i, % Efficacy) / PDE Profiling (IC₅₀)
cAMP NCI (EC₅₀)
Calcium Mobilization NCI (EC₅₀)

Confirmatory Assays

GPCR Profiling (EC₅₀)

SP= Single Point
CRC= Concentration Response Curve