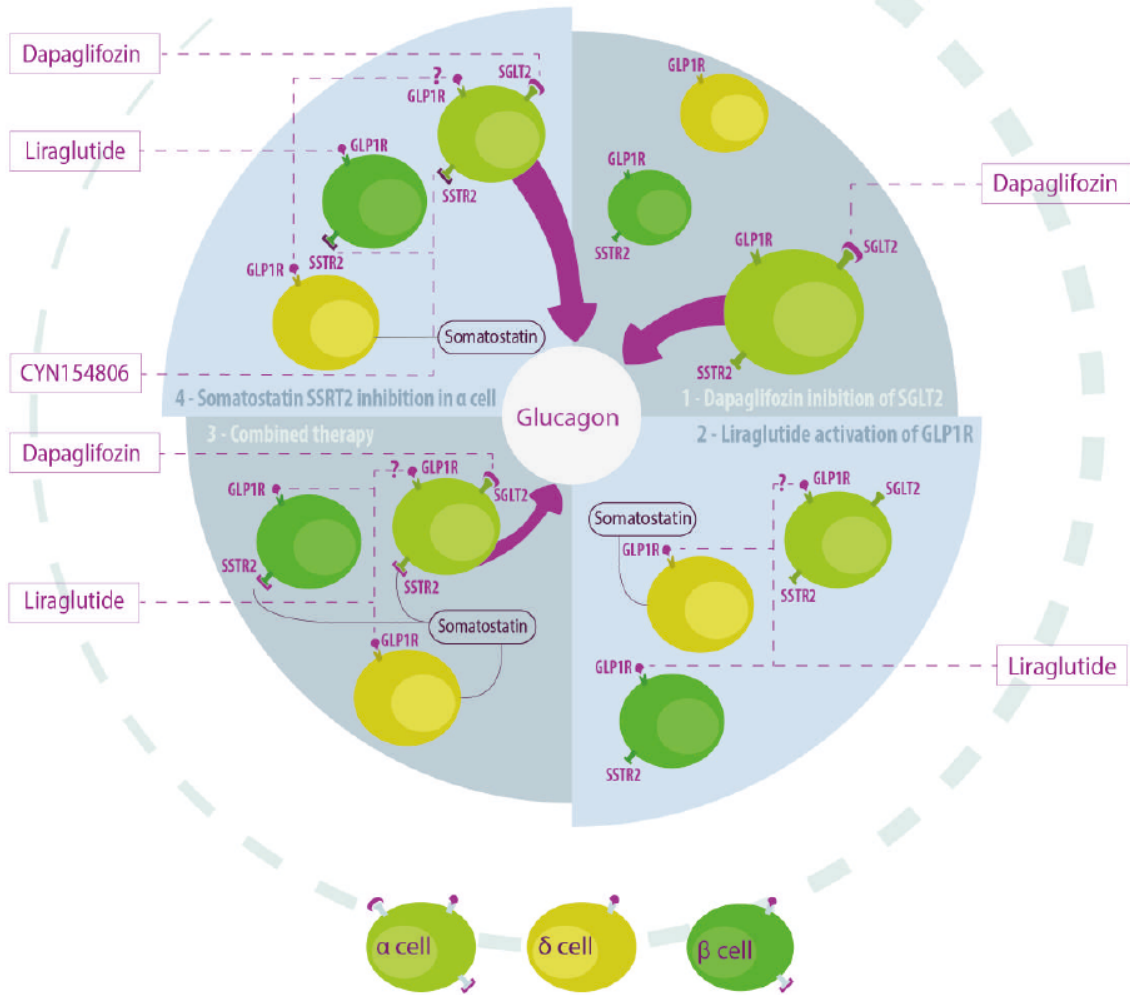


MECHANISM OF ACTION in HUMAN ISLETS in NORMOGLYCEMIC CONDITIONS



Summary of mechanism of action in human islets in normoglycemic conditions.

(1) SGLT2 inhibition by dapagliflozin promotes glucagon secretion by the pancreatic alpha cells (2) GLP1R activation by liraglutide induces somatostatin secretion in delta cells, without any effect on insulin secretion in beta cells. The role of GLP1R on alpha cells is unknown. (3) Somatostatin acts on SSTR2 present on pancreatic alpha cells to attenuate glucagon secretion induced by dapagliflozin (4) Selective inhibition of SSTR2 in alpha cells by the specific inhibitor CYN154806 reversed the glucagon lowering effect of somatostatin.