The Incretin System & Incretin-Targeting Agents

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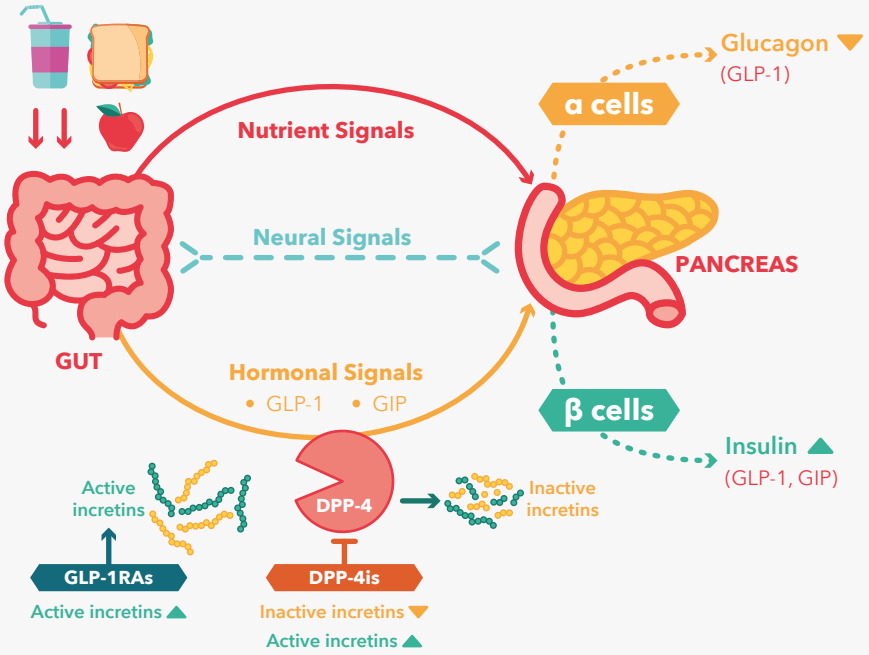
Radcliffe Medical Education

Incretin mode of action[1]

- After meal ingestion, the intestine signals to the pancreas via **GLP-1** and **GIP** hormones
- These incretin hormones have two major effects:
  - Increase glucose secretion in beta cells
  - Supress glucagon secretion from alpha cells
  - In T2DM, incretins are reduced or absent



The incretin signal can be prolonged therapeutically:[2]

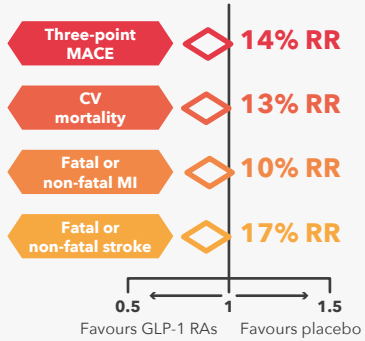
- **GLP-1 RAs**: Mimic the action of endogenous GLP-1
- **DPP-4i**:Prevent the DPP-4 enzyme from degrading endogenous GLP-1 and GIP

Properties of Incretin-Based Therapies

	DPP-4is	GLP-1 RAs
Administration route		
↑ GLP-1 levels	(meal-related)	
↑ GIP levels	(meal-related)	
Effect on HbA_{1c}	0.6 to 0.8%	1 to 2%
Effect on BW		
Hypoglycemia risk		
Side effects	uticaria	vomiting, nausea, diarrhea
CV protection		

CV benefits for GLP-1 RAs: What do the data tell us?

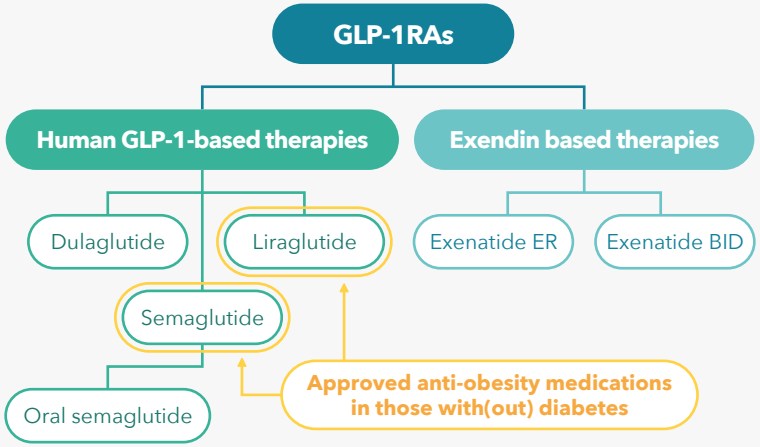
Pooled data set from 8 CV outcome trials with GLP-1 RAs suggest significant reductions in CV events compared with placebo[3]



Main available GLP-1 RA formulations[4]

GLP-1RAs are:

- Available in different formulations
  - **Weekly**: **Dulaglutide** and **injectable semaglutide**, and **Exenatide ER**
  - **Daily**: **liraglutide**, **oral semaglutide**
    - Semaglutide and liraglutide are also available at higher doses as anti-obesity medications in those with(out) diabetes
  - **Twice daily**: **Exenatide BID**
- Indicated for patients with T2DM who have prevalent CVD



Abbreviations: BID, twice daily; BW, body weight; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; DM, diabetes mellitus; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GIP, gastric inhibitory polypeptide ; GLP-1, glucagon-like peptide-1; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA_{1c}, Hemoglobin A_{1c}; RR, relative reduction; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2DM, type 2 diabetes mellitus;

References: **1.** Creutzfeldt W. Diabetologia. 1979;16:75-85. **2.** Gilbert MP et al. *Front Endocrinol* (Lausanne). 2020;11:178. **3.** Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662. **4.** Sharma D et al. *Biomed Pharmacother*. 2018;108:952-962.