Nutrient Stimulated Hormone Based Pharmacotherapy

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- Assistant Professor, Internal Medicine
- Division Direction, Obesity Medicine

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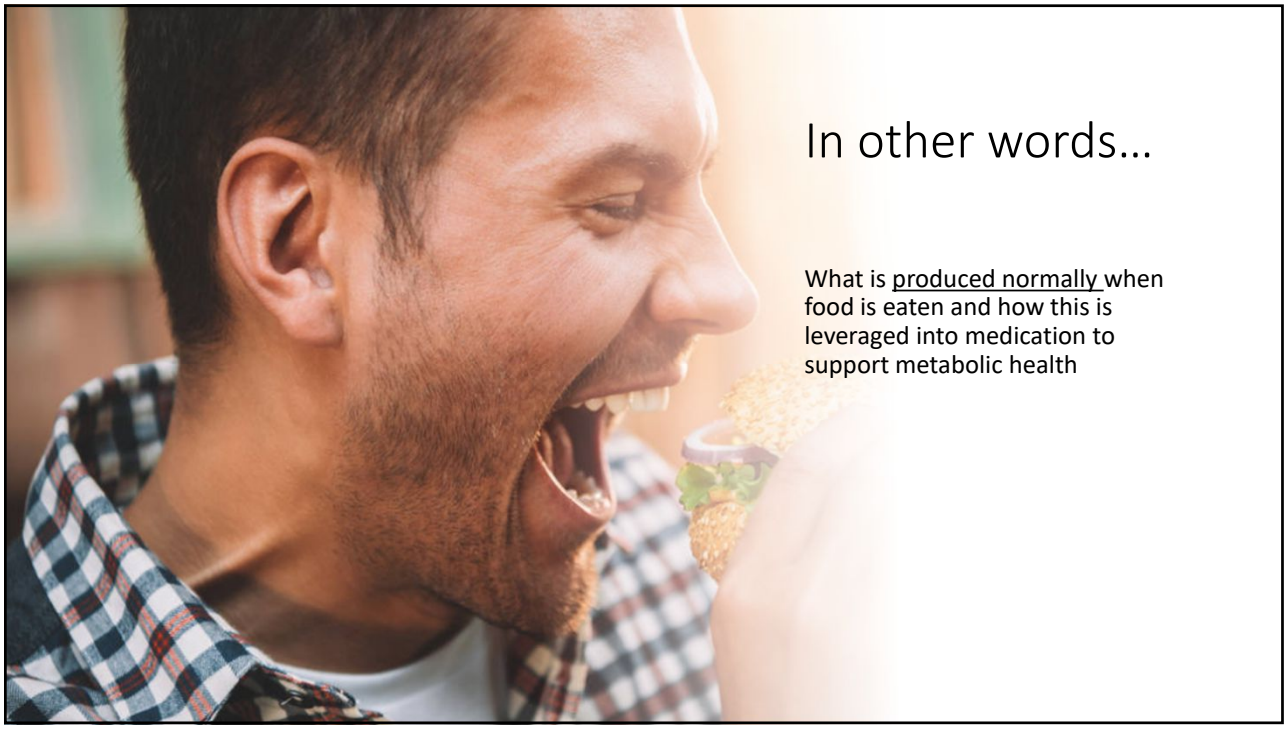

In other words…

What is produced normally when food is eaten and how this is leveraged into medication to support metabolic health

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The Incretin Effect

- First proposed by Dr. Werner Creutzfeldt, Gastroenterologist
  - Early observations that insulin secretion was two to three times higher after oral glucose intake than that after an isocaloric intravenous glucose administration.
  - The incretin effect was estimated to account for approximately 50% - 70% of the postprandial insulin responses in healthy individuals.

Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Front Endocrinol (Lausanne). 2024 Jul 24;15:1431292.

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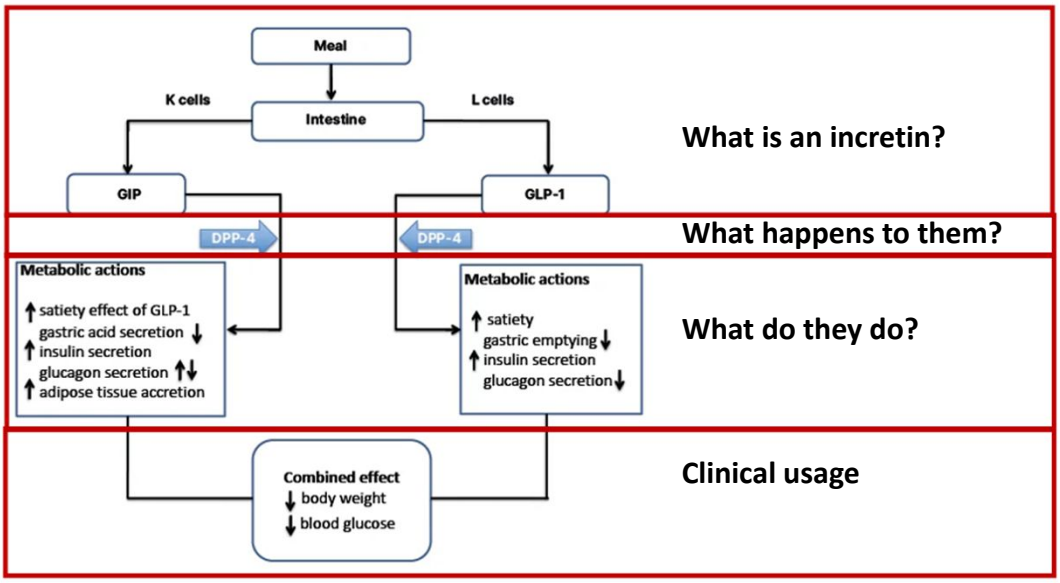

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What is an incretin?

- Incretin = hormone produced by the **gut** in **response to a meal** that **stimulates insulin** to function
  - Production - enhance the glucose-stimulated insulin secretion in β cells via activation of cAMP/PKA signaling pathways following binding to their G protein–coupled receptors
  - Release
  - Sensitivity

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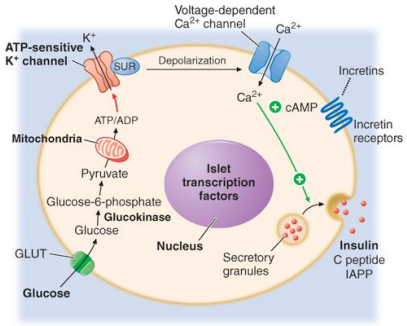

Schematic diagram of glucose-stimulated insulin release from a β cell. Glucose enters the β cell via GLUT–mediated diffusion. Glucose metabolism, the first step of which is controlled by glucokinase, results in ATP production. Cytosolic ATP, sensed by the sulfonylurea receptor (SUR) subunit of ATP-dependent K^+ channels (K_{ATP}), blocks the K_{ATP} channels and thus K^+ efflux, resulting in cell depolarization. This allows Ca^{2+} to enter via voltage-dependent calcium channels, stimulating the exocytosis of insulin-containing secretory granules. (Redrawn, with permission, from Kasper D et al, eds. Harrison's Principles of Internal Medicine, 19th ed. McGraw-Hill, 2015.)

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The Incretins

GI Lumen

- GIP
- GLP-1

Pancreatic Production

- Glucagon
- Amylin

Incretin = hormone produced by the **gut** in **response to a meal** that **stimulates insulin** to function

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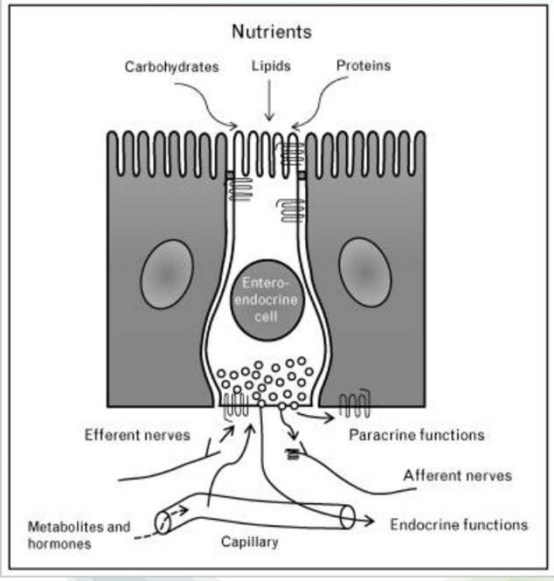
Where do they come from?

- Enteroendocrine Cells (EECs)= Incretin Production Cells embedded in intestinal lining

- K Cells (duodenum)
- L Cells (ileum and colon)



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GIP

- Glucose Dependent Insulinotrophic Polypeptide
- 455-amino acid glycoprotein with a predicted molecular weight of approximately 59 kDa
- Produced by K cells in the stomach and duodenum
- Stimulated by **Fat and carbohydrate intake**
- Among the tissues and organs crucial in regulating glucose and lipid metabolism, pancreas, brain, and adipocytes express GIP receptors (GIPRs)

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GLP-1

- Glucagon Like Peptide – 1
- Produced by L cells in the lower GI tract, ileum and colon
- 463 amino acids and has a molecular weight of 62 kDa
- GLP-1 suppresses glucagon secretion in both healthy individuals and those with T2DM under normoglycemia and hyperglycemia
- Receptors present in:
  - Pancreas
  - Brain
  - GI Tract

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Glucagon

- Glucoregulartory hormone that counteracts insulin by:
  - Stimulating hepatic glucose production
  - Hepatic lipolysis
  - Increase energy expenditure

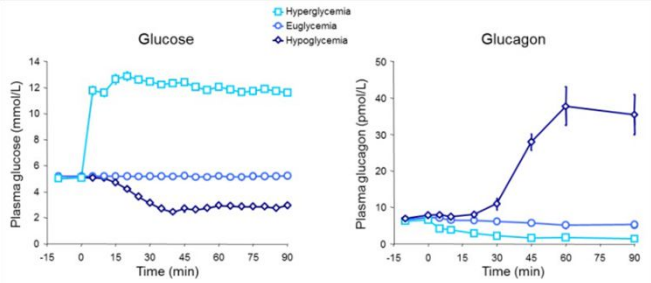

Figure 3.

Glucagon concentrations in response to hypoglycemia, euglycemia, and hyperglycemia.

Feingold KR, Adler RA, Ahmed SF, et al., editors. South Dartmouth (MA): MDText.com, Inc.; 2000

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Amylin

- Release from pancreatic beta cells
- Acts centrally to suppress appetite
- Delays gastric emptying

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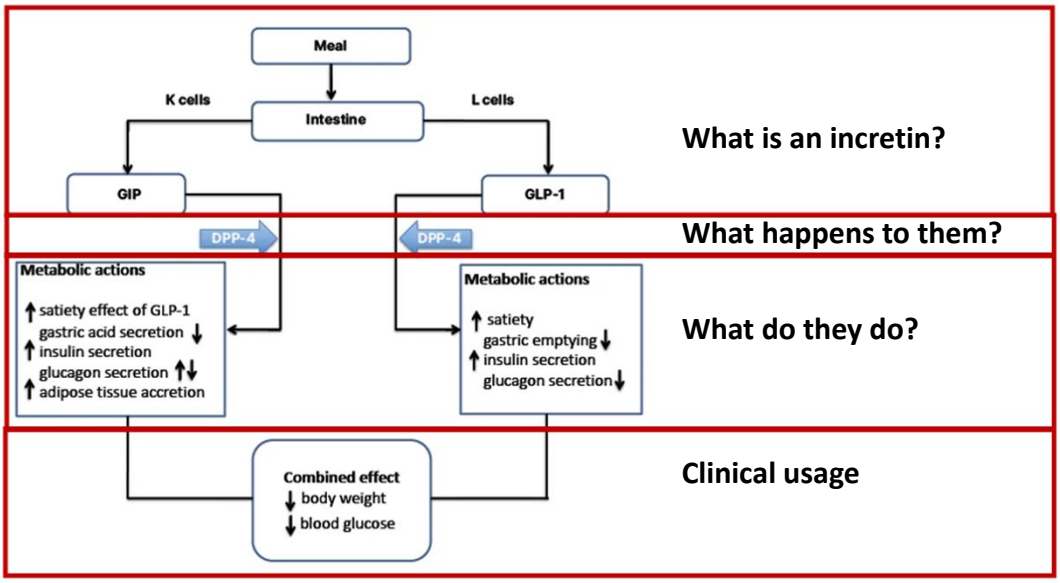

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What happens to them in vivo?

- Once secreted, both endogenous GIP and GLP-1 undergo rapid degradation into the biologically inactive metabolites. This degradation is catalyzed by the ubiquitous serum enzyme dipeptidyl peptidase 4 (DPP-4), which is produced both locally in the intestine and by circulating white blood cells.

- Both endogenous GIP and GLP-1 have very short half-lives, **measured in minutes**

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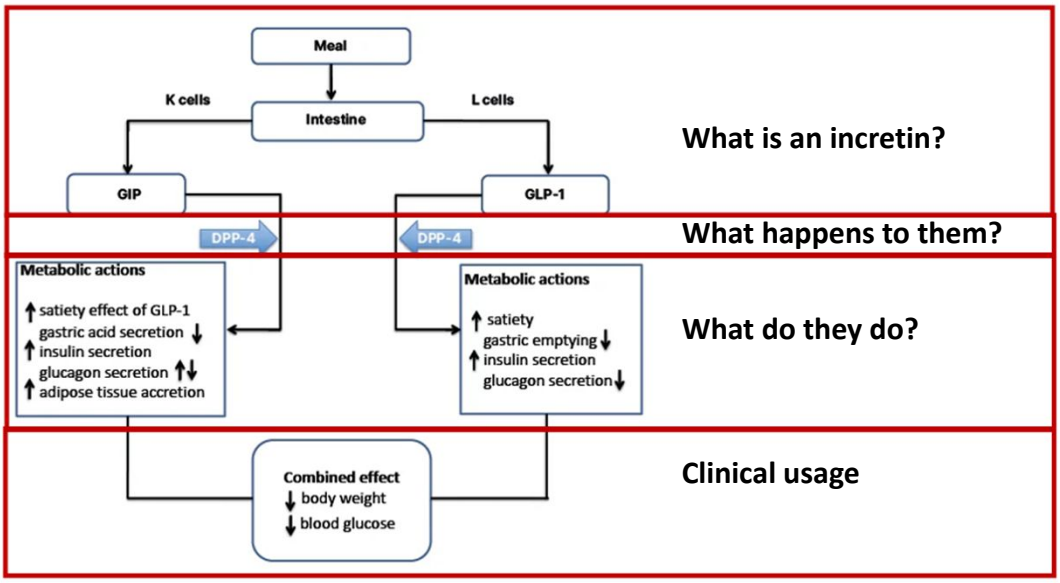

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What do incretins do?

1. Bolster insulin secretion and survival of pancreatic Beta cells
2. Modulating glucagon release by pancreatic alpha cells in response to hyperglycemia
3. Act centrally to increase satiety
4. Slowing gastric emptying
5. Regulate lipid and glucose metabolism through effects on adipose tissue and liver
6. Reduce systemic BP

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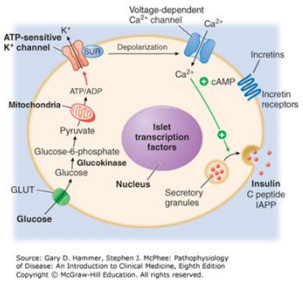
Effect on Pancreatic Beta cells (insulin)

- Act with glucose to enhance insulin gene transcription, mRNA stability, insulin biosynthesis, and insulin secretion
- GIP – **modulates** insulin release. Most active with mild hyperglycemia, elevated with high fat meals
- GLP-1 – stimulates release of insulin



Source: Gary D. Hammer, Stephen J. McPhee: Pathophysiology of Disease: An Introduction to Clinical Medicine, Eighth Edition
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Schematic diagram of glucose-stimulated insulin release from a β cell. Glucose enters the β cell via GLUT–mediated diffusion. Glucose metabolism, the first step of which is controlled by glucokinase, results in ATP production. Cytosolic ATP, sensed by the sulfonylurea receptor (SUR) subunit of ATP-dependent K^+ channels (K_{ATP}), blocks the K_{ATP} channels and thus K^+ efflux, resulting in cell depolarization. This allows Ca^{2+} to enter via voltage-dependent calcium channels, stimulating the exocytosis of insulin-containing secretory granules. (Redrawn, with permission, from Kasper D et al, eds. Harrison's Principles of Internal Medicine, 19th ed. McGraw-Hill, 2015.)

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Effect on pancreatic alpha cells (glucagon)

- GIP increase glucagon release
  - Glucose dependent
  - Hyperglycemia – more effect on insulin release
  - Normoglycemia – more effect on glucagon release
- GLP-1 suppressing glucagon secretion
  - Glucose dependent
  - Hyperglycemia – suppressed
  - Normoglycemia – suppressed
  - Hypoglycemia – NOT suppressed

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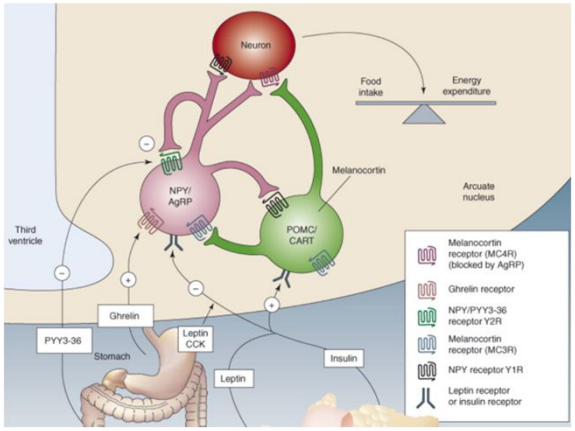
Act Centrally to increase satiety

Multiple mechanisms:

1. Satiety is primarily controlled by anorexigenic pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons in the ARH, resulting in the release α-melanocyte-stimulating hormone and a decrease of food intake

- GLP-1 increases POMC expression

2. Vagal nerve stimulation



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Act Centrally to increase satiety

- GIPR in central nervous system but not produced in the CNS.
- GLP-1 peptide is present and GLP-1R are found in the Hypothalamus

More to learn here.
We know that this is important because knockout mice have glucose lowering benefit but no appetite change/ weight reduction with incretin therapy

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Slow Gastric Emptying

- GIP – unclear, likely not linked to slowing
- GLP-1 – signaling via vagal nerve. Doses that induce gastric emptying 1000x lower that those required to increase satiety (rodent studies)
  - Timing vs. concentration

Imeryüz N, Yeğen BC, Bozkurt A, Coşkun T, Villanueva-Peñacarrillo ML, Ulusoy NB. Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent-mediated central mechanisms. Am J Physiol. 1997 Oct;273(4):G920-7. doi: 10.1152/ajpgi.1997.273.4.G920. PMID: 9357836.

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Regulate lipid and glucose metabolism

Adipose Tissue

- GIP – receptors on adipose tissue
  - Stimulates release of Lipoprotein lipase (LPL) which clears triglycerides and FFA from circulation
- GLP-1 – indirect effects
  - Increases sympathetic tone favoring lipolysis

** Synergistic

Hepatic Tissue

- GIP – indirect
- GLP-1 – indirect
  - Change in signaling from adipocytes and decreased FFA circulation promotes less adipose accumulation

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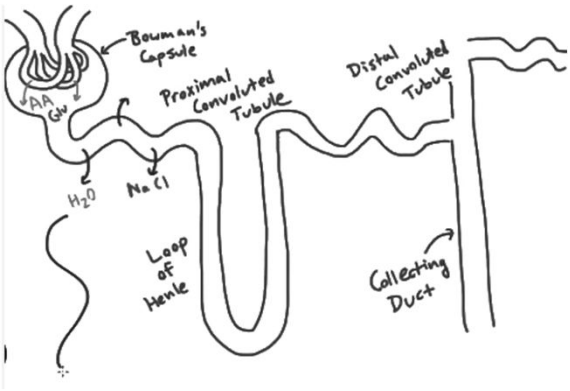
Reduce systemic BP

- GLP-1 – decreases Na and water reabsorption in proximal tubule.
- GIP – relationship has not been identified



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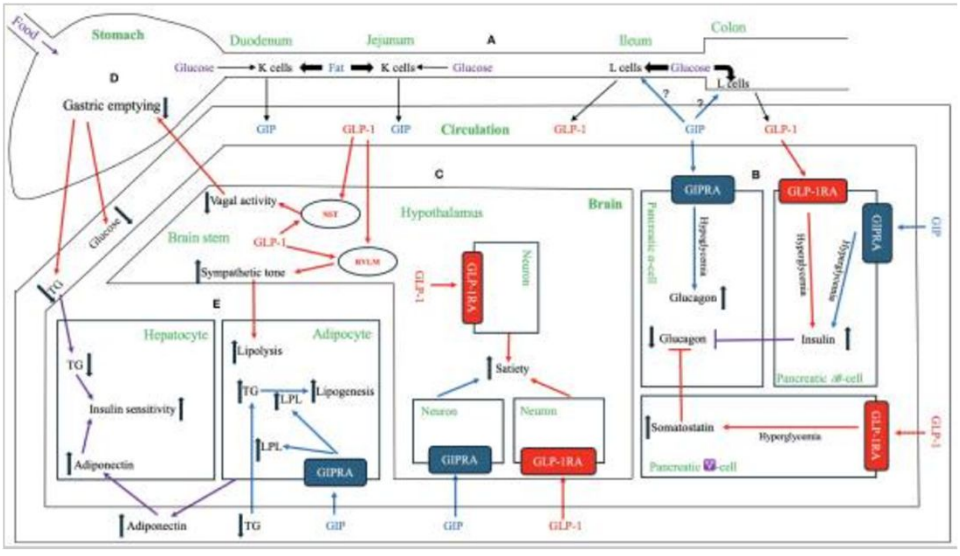

Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Front Endocrinol (Lausanne). 2024 Jul 24;15:1431292. doi: 10.3389/fendo.2024.1431292. PMID: 39114288; PMCID: PMC11304055.

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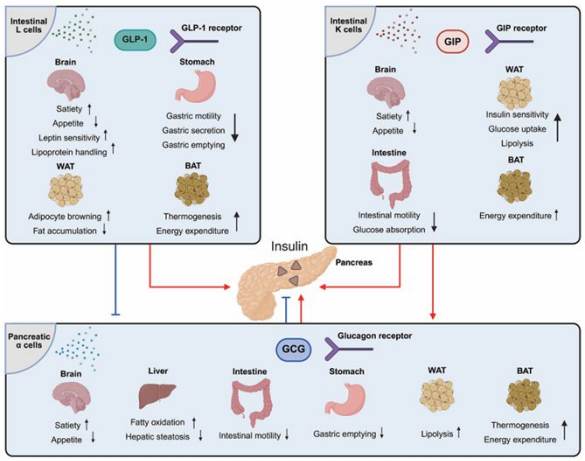

Fig. 1. Overview of the proposed routes of action of the incretin effect (e.g., GLP-1, GIP). Direct central effects on brain centers involved in the regulation of appetite and satiety. Improved lipoprotein handling via the porto-vagal axis. Increased energy expenditure through activation of thermogenesis in brown adipose tissue. Increased sensation of fullness via induced gastric emptying. Increased insulin release from the pancreas, with improved downstream glucose handling. Reduced glucagon release with improved hepatic glucose metabolism. Adapted with from Jiang *et al.* (2024).[9] Created with BioRender. BAT, brown adipose tissue; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; WAT, white adipose tissue; ↑, increase; ↓, decrease.

Phillips, Richard et al. Nutrtient Stimulated Hormone Based Therapies. *Journal of Clinical and Translational Hepatology* 2025;13(12):1060-1066

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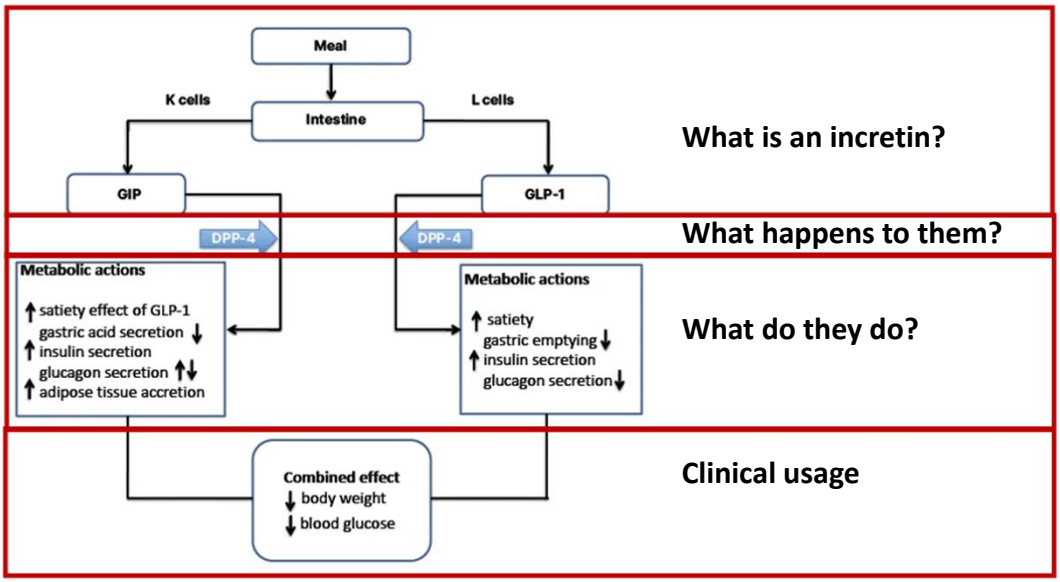

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Magic Pill?

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The Challenge

How to make it last

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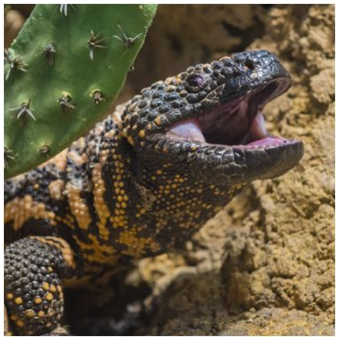
Exendin-4

- Studies at NIH in 1980s showing inflammation of the pancreas in response to certain reptiles' venom
- Gila Monster – Exendin-4. Very similar to GLP-1 but with much longer ½ life in vivo
- Stimulates insulin only when blood glucose is high
- Resistant to DPP-4



Dr. John Eng's research found that the saliva of the Gila monster contains a hormone that treats diabetes better than any other medicine. Diabetes in Control. Sept. 18, 2007.

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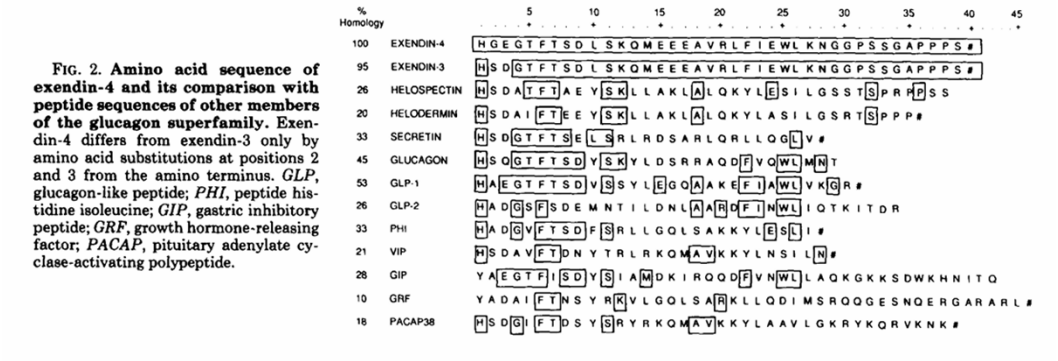

FIG. 2. **Amino acid sequence of exendin-4 and its comparison with peptide sequences of other members of the glucagon superfamily.** Exendin-4 differs from exendin-3 only by amino acid substitutions at positions 2 and 3 from the amino terminus. *GLP*, glucagon-like peptide; *PHI*, peptide histidine isoleucine; *GIP*, gastric inhibitory peptide; *GRF*, growth hormone-releasing factor; *PACAP*, pituitary adenylate cyclase-activating polypeptide.

% Homology		5 10 15 20 25 30 35 40 45
100	EXENDIN-4	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS#
95	EXENDIN-3	HSDGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS#
26	HELOSPECTIN	HSDATFTAEYSKLLAKLALQKYLESILGSSTSPRPPSS
20	HELODERMIN	HSDAIFTEEYSKLLAKLALQKYLASILGSRTSPPP#
33	SECRETIN	HSDGTFTSELSRLRDSARLQRLLQGLV#
45	GLUCAGON	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT
53	GLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR#
26	GLP-2	HADGSFSDEMNTILDNLAARDFINWLIQTKITDR
33	PHI	HADGVFTSDFSRLLGQLSAKKYLESLI#
21	VIP	HSDAVFTDNYTRLRKQMAVKKYLNSILN#
28	GIP	YAEGTFISDYSIAMDKIRQQDFVNWLLAQKGKKSDWKHNITQ
10	GRF	YADAIFTNSYRKVLGQLSARKLLQDIMSRQQGESNQERGARARL#
18	PACAP38	HSDGIFTDSYSRYRKQMAVKKYLAAVLGKRYKQRVKNK#

Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Eng J, Kleinman WA, Singh L, Singh G, Raufman JP. Journal of Biological Chemistry. 1992;267(11):7402-7405.

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First Incretin used pharmacologically - **Exenatide**

- FDA approved for DMII 2005

Agent (trade name)	Maximal dosing regimen approved	FDA-approved indication for T2DM (year of approval)		FDA-approved indication for obesity (year of approval)		FDA-approved indication for cardiovascular risk reduction (year of approval)
		Adult	Adolescent	Adult	Adolescent	
Exenatide IR (Byetta®)	10 µg twice daily injection	Yes[1] (2005)	No	No	No	No
Exenatide ER (Bydureon®)	2 mg once weekly injection	Yes (2012)	No	No	No	No
Lixisenatide[2] (Adlyxin®)	20 µg once daily injection	Yes (2016)	No	No	No	No

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Exenatide

Table 10: 30-Week Comparator-Controlled Trial of BYETTA used in Combination with Insulin Glargine and Metformin

	Titrated Insulin Lispro TID + Titrated Insulin Glargine	BYETTA 10 mcg* BID + Titrated Insulin Glargine
Intent-to-Treat Population (N)	312	315
HbA_{1c} (%), Mean		
Baseline	8.2	8.3
Change at Week 30†#	−1.1	−1.1
Difference from Insulin Lispro†# (95% CI)		−0.0 [−0.2, 0.1]
Body Weight (kg), Mean		
Baseline	89.3	89.9
Change at Week 30†#	1.9	−2.6
Difference from Insulin Lispro†# (95% CI)		−4.5 [−5.2, −3.9]
Fasting Serum Glucose‡ (mg/dL), Mean		
Baseline	126	129
Change at Week 30†#	5	−7
Difference from Insulin Lispro†# (95% CI)		−12 [−19, −4]

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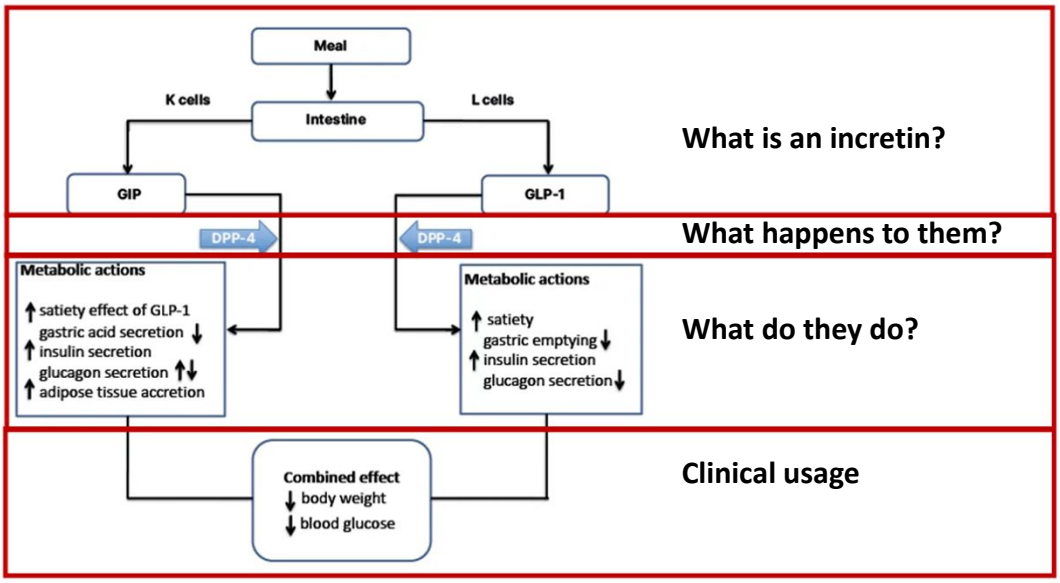

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GLP-1 Medications

Medications/ FDA approval	Diabetes	Obesity	SECONDARY Prevention of CV Disease	Moderate – Severe OSA	MASH Fibrosis 2-3
	Requires Dx of DMII	BMI >27 with comorbid conditions or BMI >30	History of heart attack, stroke, or peripheral vascular disease	Requires AHI >15. Must provide sleep study results with PA	Biopsy proven
Liraglutide	Victoza	Saxenda			
Semaglutide	Ozempic	Wegovy	Wegovy		Wegovy
Semaglutide oral	Rybelsus	Wegovy	Wegovy		
Dulaglutide	Trulicity				
Tirzepatide	Mounjaro	Zepbound		Zepbound	

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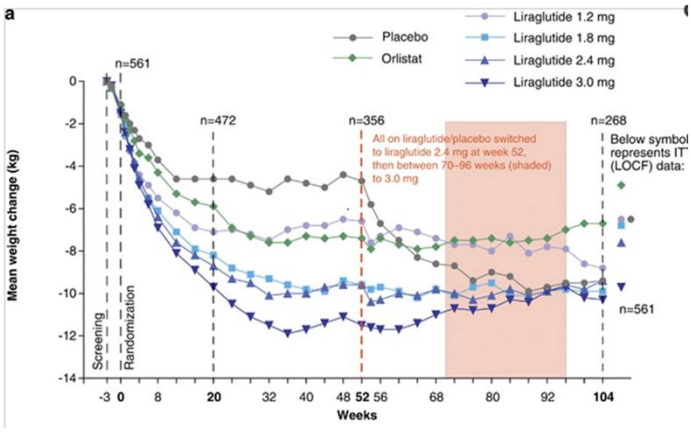
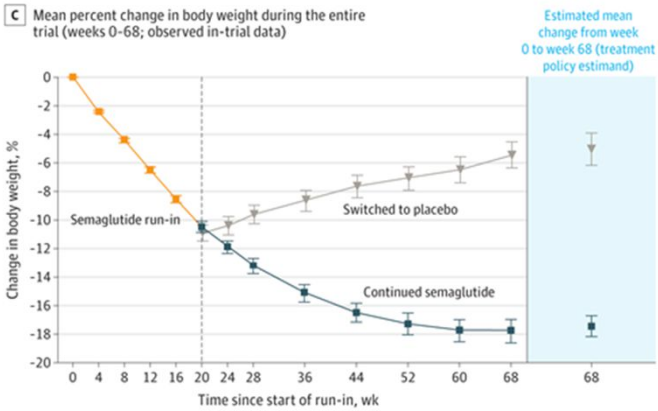
Liraglutide

- FDA approved in 2010 for diabetes management
- FDA approved in 2014 for obesity management
- fatty acid acylation of lysine 26 to facilitate serum albumin noncovalent binding to prolong their plasma half-lives
- MOA – GLP-1



Semaglutide

- FDA approved in 2017 for diabetes management
- FDA approved in 2021 for obesity management
- Substitution of alanine residue with a non-coded amino acid, 2-aminoisobutyric acid (Aib) at position 8, shielding against DPP-4-mediated N-terminal proteolysis while preserving GLP-1R affinity
- MOA – GLP-1



Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA.* 2021;325(14):1414–1425. doi:10.1001/jama.2021.3224

Semaglutide, oral

- FDA approved in 2019 for diabetes management
- FDA approved in 2025 for obesity management
- In this oral formula, semaglutide is non-covalently linked to sodium N-[8-(2-hydroxybenzoyl) aminocaprylate] (SNAC), which shields the peptide from enzymatic and acidic degradation in the stomach
- MOA: GLP-1

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Semaglutide, oral

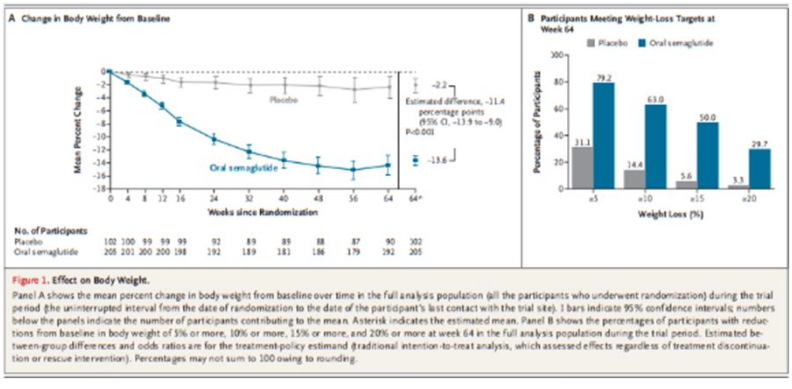

Figure 1. Effect on Body Weight.

Panel A shows the mean percent change in body weight from baseline over time in the full analysis population (all the participants who underwent randomization) during the trial period (the uninterrupted interval from the date of randomization to the date of the participant's last contact with the trial site). I bars indicate 95% confidence intervals; numbers below the panels indicate the number of participants contributing to the mean. Asterisk indicates the estimated mean. Panel B shows the percentages of participants with reductions from baseline in body weight of 5% or more, 10% or more, 15% or more, and 20% or more at week 64 in the full analysis population during the trial period. Estimated between-group differences and odds ratios are for the treatment-policy estimand (traditional intention-to-treat analysis, which assessed effects regardless of treatment discontinuation or rescue intervention). Percentages may not sum to 100 owing to rounding.

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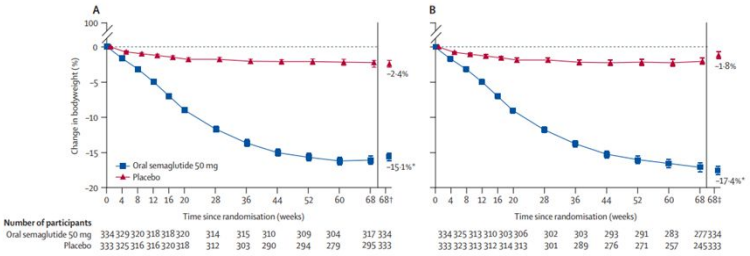
PIONEER study

Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial

*Filip K Knop, Vanita R Aroda, Ruben D do Vale, Thomas Holst-Hansen, Peter N Laursen, Julio Rosenstock, Domenica M Rubino, W Timothy Garvey, for the OASIS 1 Investigators**



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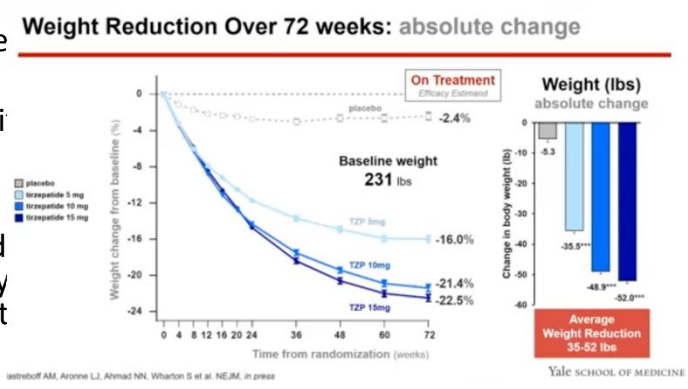
Tirzepatide

- FDA approved in 2022 for diabe management
- FDA approved in 2023 for obesi management
- 39-amino acid peptide acylated with a C20:0 fatty diacid moiety lysine residue at position 20 wit molecular weight of 4.8 kDa
- MOA: GLP-1 and GIP



Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM. *in press*

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Liraglutide	Victoza	Saxenda			
Semaglutide	Ozempic	Wegovy 	Wegovy 		Wegovy 
Semaglutide oral	Rybelsus 	Wegovy 	Wegovy 		
Dulaglutide	Trulicity 				
Tirzepatide	Mounjaro 	Zepbound		Zepbound	

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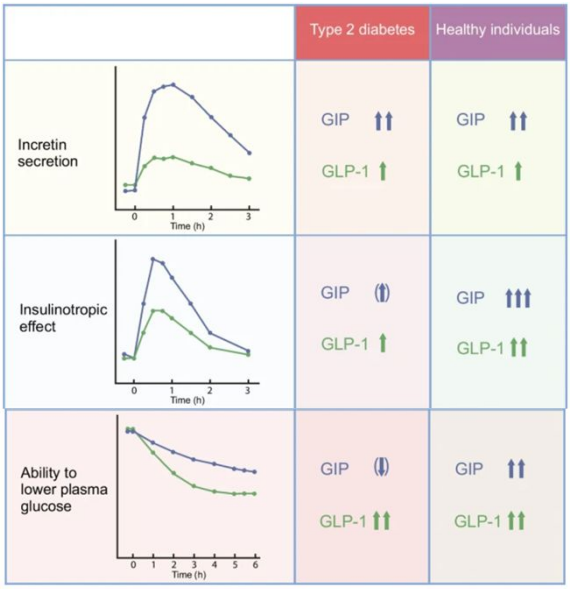
Incretin function with DMII



The incretin effect was estimated to account for approximately 50% - 70% of the postprandial insulin responses in healthy individuals and may be substantially reduced to 20% – 30% in individuals with type 2 diabetes mellitus

Nauck, M.A., Müller, T.D. Incretin hormones and type 2 diabetes. *Diabetologia* **66**, 1780–1795 (2023).

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Future Directions

- Dual and triple incretin therapy
- Sema/cargrilintide
- Glucagon/ GLP-1 (survodutide)
- GIP/GLP-1/ glucagon (Retatrutide)
- Orforglipron

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- Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Front Endocrinol (Lausanne). 2024 Jul 24;15:1431292. doi: 10.3389/fendo.2024.1431292. PMID: 39114288; PMCID: PMC11304055.

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