

OZEMPIC: RISE OF THE GLP-1 MIMICS

OBESITY TRENDS (CDC DATA)

- 1990: 10-20% obesity (US Adults)
- 2011: 20-30% obesity (US Adults)
- 2022: 300-40% obesity (US Adults)

- 40 million diabetics
- 100 million pre-diabetics

GLP-1 (GLUCAGON LIKE PEPTIDE 1)

- Many tissues create “proglucagon”
- Proglucagon is translationally modified to many proteins including GLP-1

GLP-1 PRODUCING CELLS

- **Ileum and Colon**
 - Enteroendocrine cells (L cells)
- **Central Nervous System (CNS)**
 - Neurons (not glial cells)

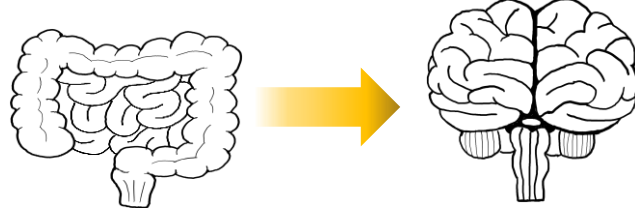
GLP-1 RECEPTORS

- **Many** organs/tissues
 - Brain, pancreas, liver, kidneys heart, stomach, muscle, bone, etc.

GLP-1 ACTIONS

- **CNS**
 - ↑ Learning & Memory
 - ↑ Neuroprotection
 - ↓ **Food Intake**
 - ↓ Water Intake
 - ↓ Inflammation
 - ↓ Reward Behavior
 - ↓ Palatability
 - ↓ Apoptosis
- **Pancreas**
 - ↑ Insulin Synthesis
 - ↑ **Insulin Secretion**
 - ↓ Glucagon Secretion
 - ↑ β Cell proliferation
 - ↓ Apoptosis
 - ↑ β Cell survival
- **Liver**
 - ↓ Gluconeogenesis
 - ↓ Steatosis
- **Stomach**
 - ↓ Gastric Emptying
 - ↓ **GI Motility**

Gut GLP-1 receptors communicate with the brain via vagal afferent nerves.



Müller, T. D., Finan, B., Bloom, S. R., D'Alessio, D., Drucker, D. J., Flatt, P. R., ... & Tschöp, M. H. (2019). Glucagon-like peptide 1 (GLP-1). *Molecular metabolism*, 30, 72-130.

- **Skeletal Muscle**
 - ↑ Insulin Sensitivity
 - ↑ Glucose Uptake
- **Kidneys**
 - ↑ Diuresis
 - ↑ Natriuresis
- **Heart**
 - ↑ Contractility
 - ↑ Cardiac Output
 - ↑ Myocyte Survival
 - ↑ Cardioprotection
 - ↑ Vasodilation
 - ↑ Glucose Uptake
 - ↑ Left Ventricular Fxn
 - ↑ APN production
 - ↑ Natriuresis

GLP-1 DEGRADATION

- Enzyme = **DPP-4** (Dipeptidylpeptidase-4)
 - Cell membranes and circulating
 - **Half-life of GLP-1 = 1-2 minutes**
- Most degraded in the intestinal enterocyte brush boarder (75%)
- Liver clears 50% of the remaining concentration
- **10-15% reach systemic circulation**

GLP-1 MIMICS (DRUGS)

- Exenatide (Byetta)
- Liraglutide (Victoza)
- Dulaglutide (Trulicity)
- Albiglutide (Tanzeum)
- Lixisenatide (Adlyxin)
- **Semaglutide (Ozempic) Half Life = 5.7 to 6.7 days**
- **Semaglutide (Rybelsus)**
- **Semaglutide (Wegovy) Half Life = 5.7 to 6.7 days**
- **Trizepatide (Zepbound)**
- Retatrutide
- Danuglipron

DRUGS

Ozempic: \$1,000 – \$1,200 per month
Wegovy: \$1,300 – \$1,500 per month
Zepbound: \$1,000 – \$1,200 per

STEP (SEMAGLUTIDE TREATMENT EFFECT IN PEOPLE WITH OBESITY)

The Semaglutide Treatment Effect in People with obesity (STEP)

- 2.4 mg semaglutide injection once/week (68 weeks)
- Mean weight loss 14.9% - 17.4% of body weight
- 69-79% of patients lost ≥ 10% body weight
- 51-64% lost ≥ 15% body weight

Chao, A. M., Tronieri, J. S., Amaro, A., & Wadden, T. A. (2023). Semaglutide for the treatment of obesity. *Trends in cardiovascular medicine*, 33(3), 159-166.

- **Improvements in cardiometabolic risk factors**, including high blood pressure, atherogenic lipids and benefits on physical function and quality of life were seen with semaglutide 2.4 mg.
- The safety profile of semaglutide 2.4 mg consistent across trials, primarily GI adverse events.

ADVERSE EFFECTS

Any: 90%

Nausea: 44%

Diarrhea: 32%

Vomiting: 25%

Constipation: 23%



GLP-1 – PHYSIOLOGY VERSUS PHARMACOLOGY

GLP-1 has a 1–2-minute half-life in vivo

Fasting

- **<2 pmol/L** (active molecule) 5-10 pmol/L
- Tonicly secreted into circulation under basal conditions

Fed

- **5-10 pmol/L** (active molecule)
- Up to 40 pmol/L including metabolites via DPP-4 degradation)
- Peaks in 30 – 60 minutes
- Returns to baseline in 90-120 minutes
- Lipids lead to a later, but more prolonged (>120 minutes) increase

Wegovy (semaglutide) = 75 nmol/L steady state with a 7-day half-life

10,000 – 37,500 times the concentration

100 times longer-lived

OTHER CONCERNS

DECREASED LEAN MASS (SKELETAL MUSCLE)

- Up to 40% of the weight lost may be from lean mass (sarcopenia)
- Skeletal muscle plays a huge role in insulin sensitivity and glucose clearance

SYMPATHETIC/PARASYMPATHETIC TONE

- GLP-1 increases heart rate
- **~Inhibition of the parasympathetic nervous system**
- **~Activation of the sympathetic nervous system** McLean, et al. (2021)

DECREASED NUTRITION

- Examples: Dietary Fiber, Protein

LACKING LONG-TERM DATA...

ADDITIONAL ONLINE CONTINUING EDUCATION (WEINERT)

- INTERMITTENT FASTING
- GUT MICROBIOTA
- GLUTEN AND CELIAC DISEASE
- MUSCLE MATTERS

<https://palmerce.learningexpressce.com/index.cfm?eventTypeID=0&categoryIDs=&q=weinert>

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