GLP-1 AGONISTS: A NEW FOUNDATION FOR CAD PREVENTION AND BEYOND?

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AGENDA:

GLP1 , Where have you been all of our lives? Tell us more!
- Discovery, physiology, function

How did you win our hearts?
- Prominent trials: LEADER, SUSTAIN-6, SELECT

Who's your friend over there?
- GIP: Similarities, differences, synergism

Do you have more friends like that?
- Upcoming Research: GIP, amylin, glucagon, others

GLP1 ,

WHERE HAVE YOU BEEN ALL OF OUR LIVES? TELL US MORE!

Discovery, Physiology [1, 2]:

1980s: Oral glucose >IV glucose Insulin secretion -> gut hormones stimulate insulin

molecular cloning

Produced by enteroendocrine cells (EECs) in SI and colon after food intake

Main actions: stimulates Glucose-dependent insulin secretion, inhibits glucagon secretion.

Rapid break down by DPP-4 (dipeptidyl peptidase-4)

1990s – 2000s: GLP-1 receptor agonists for T2DM treatment

2000s: obesity treatment (diabetics were losing wt!)

2008: FDA mandate

2010s: clinical trials, found reduction in Major adverse Cardiovascular events (MACE).

GLP 1

Functions:

Cardiovascular [3]: Receptors expressed in heart and vasculature

Endothelium: increases nitric oxide-> vasodilation -> Improves blood flow, reduces BP

Anti-inflammatory and antioxidant: reduces inflammatory markers and oxidative stress, prevent CVD progression

Heart: improves contractility, efficiency, cardiac output, reduces heart failure risks

GLP1

Functions:

Stomach/Gut

Slows gastric emptying
Inhibits gastric motility
Regulate appetite

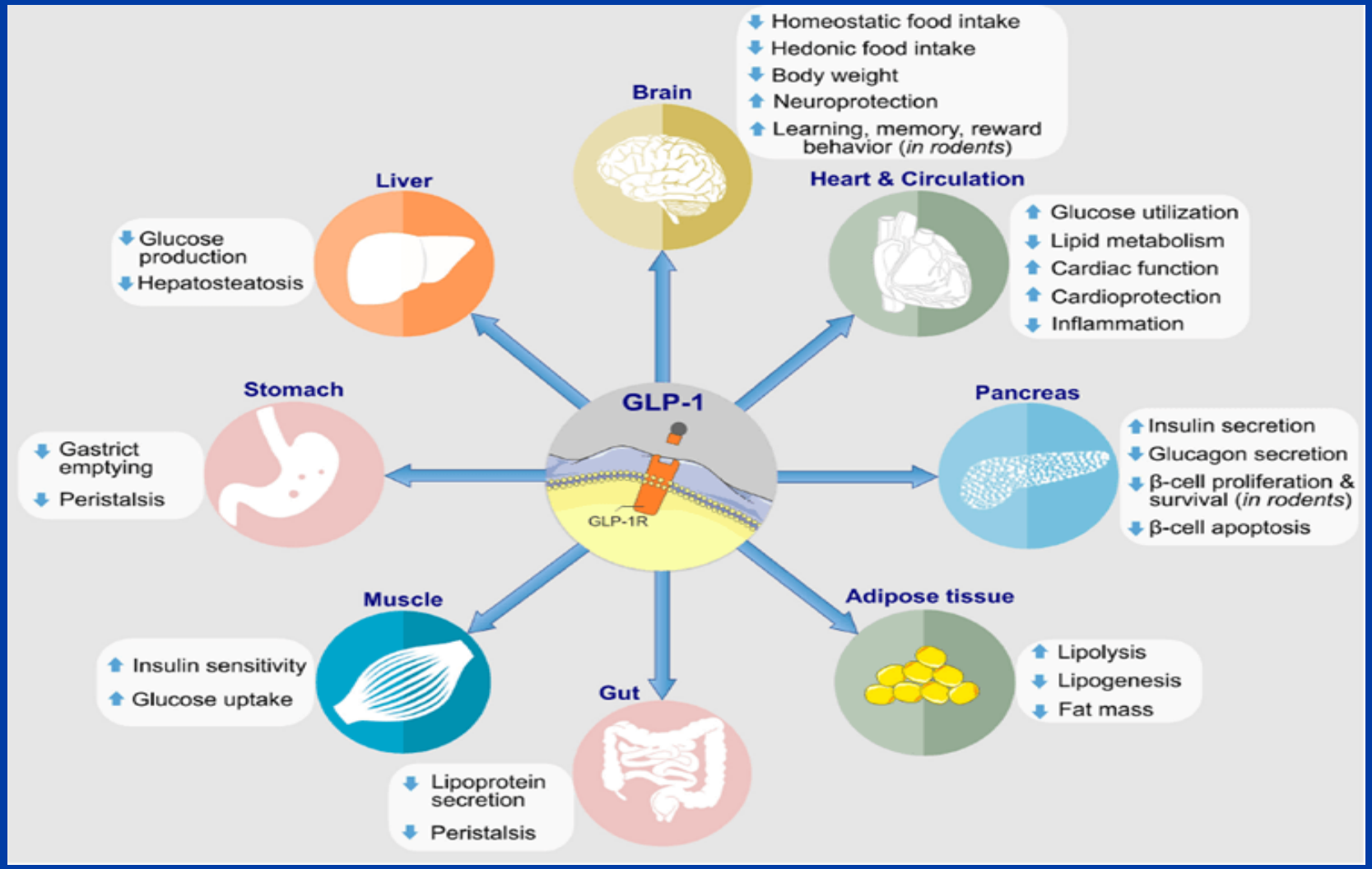
Brain

Crosses BBB, produced by brain neurons.
Diverse neural circuits and reward related behaviors,
Reduces stress and anxiety

Metabolism (DM, Obesity)

Stimulates insulin secretion
Inhibits glucagon secretion - Pancreas
Slows gastric emptying (reduce postprandial glucose)-Stomach
Increases satiety, Reduce Appetite - Hypothalamus

GLP 1


Brain
Homeostatic food intake
Hedonic food intake
Body weight
Neuroprotection
Learning, memory, reward behavior (in rodents)
Liver
Glucose production
Hepatosteatosis
Heart & Circulation
Glucose utilization
Lipid metabolism
Cardiac function
Cardioprotection
Inflammation
Stomach
Gastrict emptying
Peristalsis
GLP-1
GLP-1R
Pancreas
Insulin secretion
Glucagon secretion
β-cell proliferation & survival (in rodents)
β-cell apoptosis
Muscle
Insulin sensitivity
Glucose uptake
Adipose tissue
Lipolysis
Lipogenesis
Fat mass
Gut
Lipoprotein secretion
Peristalsis

GLP 1 RECEPTOR AGONIST

Current Medications:

GLP-1 RA

- Exenatide (Byetta)
- Liraglutide (Victoza, Saxenda)- first generic this year
- Dulaglutide (Trulicity)
- Semaglutide (Ozempic, Wegovy, Rybelsus)

GLP-1 /GIP RA

- Tirzapetide (Mounjaro, Zepbound)- first in class

HOW DID YOU WIN OUR HEARTS?

Heart disease, leading cause of death in the US, 1 in every 5

Heart disease risk factors driving prevalence:

- High blood pressure (47% of U.S. adults)
- High cholesterol (38%)
- Diabetes (11%)
- Obesity (42.4%) +Overweight (70%)

CARDIAC IMPLICTIONS

T2DM and obesity are 2 significant diseases that impact CV health.

T2DM

Elevated blood sugar: damage blood vessels

Insulin resistance: linked to HTN, HLD

Chronic inflammation: heart attacks, heart failure

Obesity

Excess body fat: HTN, HLD, insulin resistance
Heart strain: enlargement, heart failure
Chronic Inflammation: blood vessel injury, risk of atherosclerosis

Combined Impact

Increased risk of Metabolic syndrome, increasing Heart disease risk, plaque build up, with potential for MI, strokes

HOW DID YOU CAPTURE OUR HEARTS?

PROMINENT TRIALS

2008, FDA mandate all new DM meds demonstrate CV safety via clinical trials

Several trials conducted looking at CV outcomes in T2DM and Obesity/OW.

Trials revealed:

- Treatment of DM and Obesity can improve CV risk
- Direct action of GLP1 RA also seems to improve CV risk.

GLP 1
PROMINENT TRIALS

LEADER (2016) [5]:

Assessed CV safety and efficacy of **liraglutide** in patients +T2DM, +at high CV risk.
Landmark study, first to establish CV benefits of GLP1RA.
Results:

- Reduction in Primary outcome (MACE- CV death, NF MI, NF stroke) by 13%
- No increase in heart failure hospitalizations
- Improved glycemic control
- Reduction in progression of diabetic kidney disease

GLP 1
PROMINENT TRIALS

SUSTAIN-6 (2016) [6]:

Assessed CV outcomes of Semaglutide +T2DM +high CV risk.
Results: Sig reduction in primary outcome –MACE by 26%
- Non-fatal Stroke Reduction 39%
- NF MI reduction 26%
- CV death reduction: +, but not stat sig

GLP 1
PROMINENT TRIALS

SELECT (2023) [7]:

Assessed CV outcomes of Semaglutide +OW/Ob (no T2DM) +High CV risk
Results: Sig reduction of Primary outcome (MACE) by 20%
*Increased role of GLP1 RA in CVD prevention.

Medicare statement on WL meds based on this discovery:

"CMS is clarifying that AOMs that receive FDA approval for an additional medically accepted Indication…. For example, a glucagon-like peptide 1 (GLP-1) receptor agonist that receives FDA approval to treat diabetes or reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight, then it would be considered a Part D drug for those specific uses only."

PROMINENT TRIALS

	LEADER	SUSTAIN-6	SELECT
Publication year	2016	2016	2023
Medication	Liraglutide	Semaglutide	Semaglutide
Assessed	MACE	MACE	MACE
Population	+DM, +High CV risk	+DM, +High CV risk	+Obesity +High CV risk
Results (Reduction)	13%	26%	20%

GLP 1

PROMINENT TRIALS:

How was CV risk reduction achieved in the SELECT trial? Some theories:

GLP-1 effect (Semaglutide):

- Reduced inflammation
- Improved endothelial and LV function
- Plaque stability
- Platelet aggregation reduced
- Improved BP, glycemic control, lipid levels
- Reduction of excess body fat

Weight loss effect:

- Improved glucose
- Reduced CV risk factors- 10% WL improves CV risk

Decrease in fat mass effect:

- Reduced ectopic adipose tissue depots- myocardial dysfunction.
- Reduced perivascular and epicardial adipose tissue- direct adverse effects.
- Improved systemic proinflammatory and prothrombotic setting of obesity.

WHO'S YOUR FRIEND OVER THERE?

GIP: SIMILARITIES, DIFFERENCES, AND SYNERGISM

GLP1/GIP RA- (Tirzapetide) the first combination

GIP: (Gluc-dependent insulinotropic polypeptide), secreted by K cells in SI when carbs/fats ingested.[8]

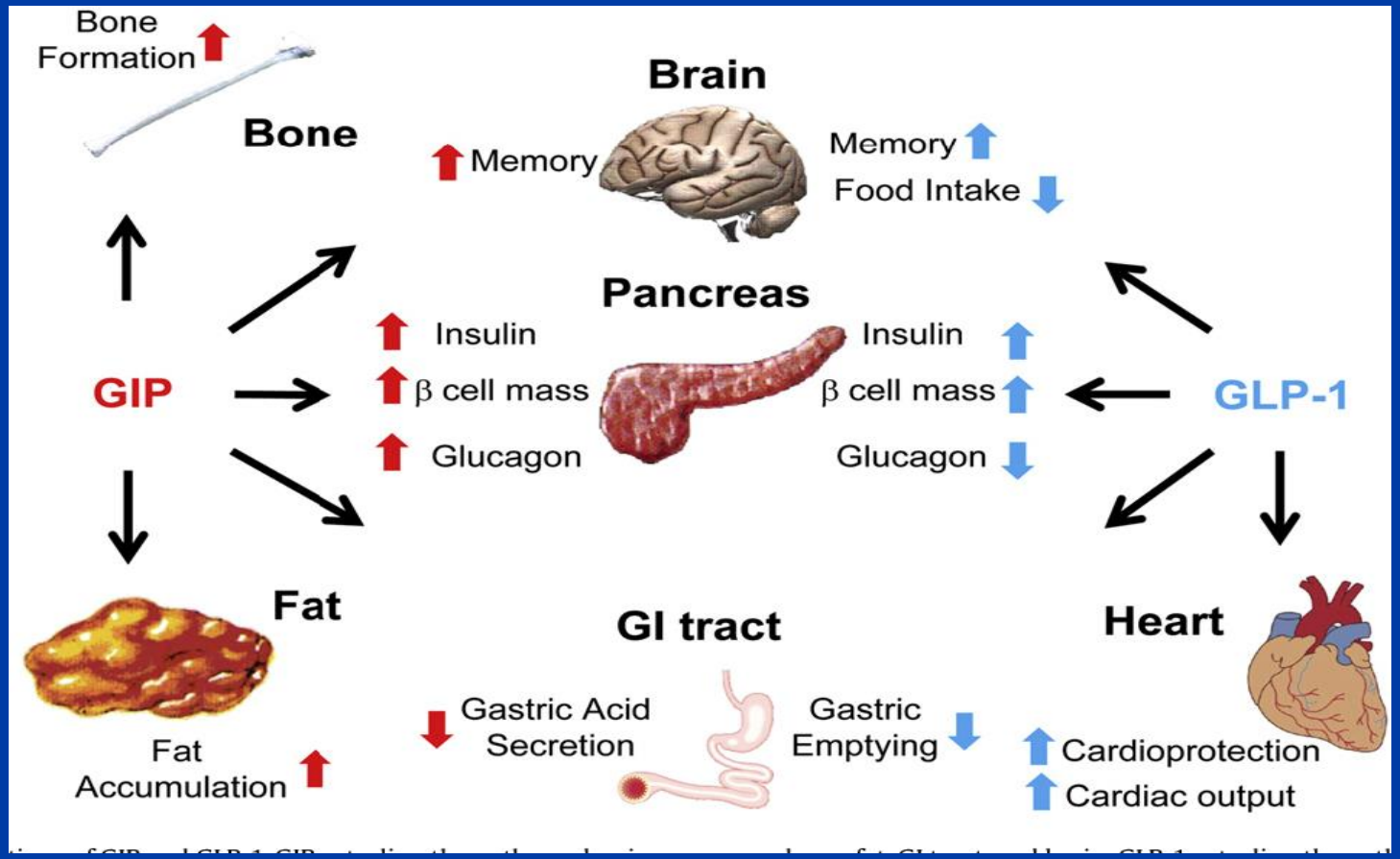
Similarities: both incretins, induce insulin secretion, expressed in different organs. [8]

Differences: GIP promotes glucagon secretion, lipogenesis, fat storage, bone formation and increased density, improved cognition and mood. [8]

Synergism: glycemic control, dramatic weight loss (up to 25%). Possibly improved cognitive function and CV function. [8]

GIP

SIMILARITIES, DIFFERENCES, AND SYNERGISM



DO YOU HAVE MORE FRIENDS LIKE THAT?

UPCOMING RESEARCH

GLP-1 in Dual, triple combos with GIP, amylin, glucagon, others.
Purpose:

- Improve effect on CVD
- Greater wt reduction, improve body composition [9]
- Treat Neurodegenerative diseases
- Mood regulation, develop anxiolytics and antidepressants [8]

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