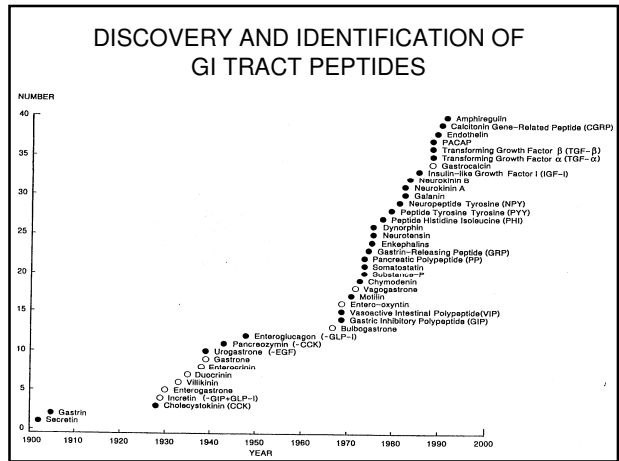
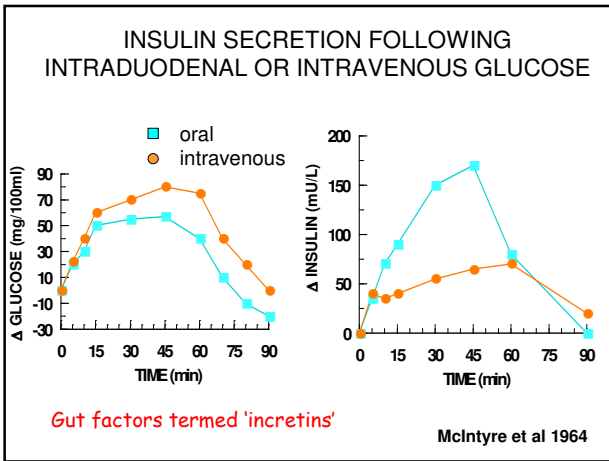


Bayliss WM & Starling EH

The mechanism of pancreatic secretion
J. Physiol 28:325-335, 1902

1. Denervated jejunum releases pancreatic juice when acidified
2. SI extracts release pancreatic juice from denervated pancreas

Blood-borne signal = secretin



THE SECRETIN FAMILY AS INCRETINS

- Secretin
- GIP
- VIP
- Glucagon
- Glucagon-like peptides
- GLP-1
- GLP-2
- glicentin
- oxyntomodulin

}

All stimulate insulin secretion in pharmacological doses

GIP, GLP-1, physiological incretins

Responsible for ~50% insulin secretion

GIP

Gastric inhibitory polypeptide
Glucose-mediated insulinotropic polypeptide

Molecular weight: 4984

Location: Duodenum, jejunum, upper small intestine

Major actions: inhibition of gastric acid secretion
stimulation of insulin secretion
insulin-like actions on lipid metabolism

GLP-1

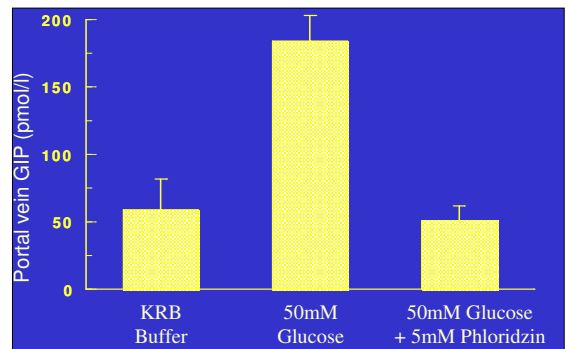
Glucagon-like peptide-1(7-36) amide

Molecular weight: approx 4000

Location: Distal small intestine, Colon

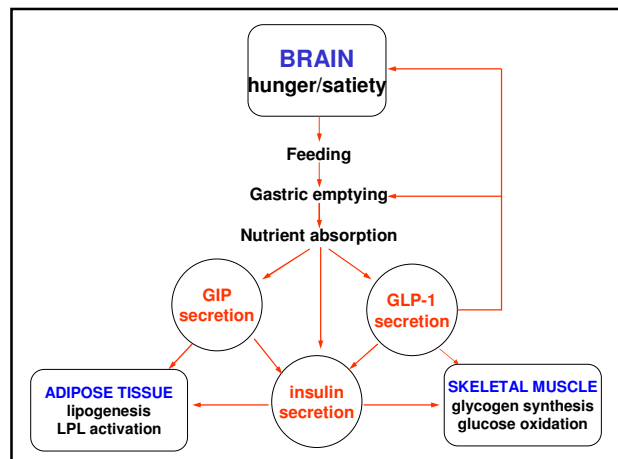
Major actions: Stimulation of insulin secretion
Inhibition of gastric emptying
Insulin-like extrapancreatic actions
Inhibitory effects on appetite

EFFECT OF PHLORIDZIN ON GIP LEVELS IN RATS FOLLOWING IN-SITU PERFUSION OF 50mM GLUCOSE



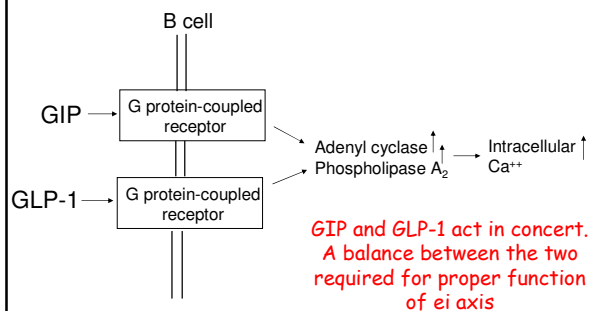
OTHER EFFECTS OF GLP-1 ON CHO METABOLISM

- Suppression of glucagon secretion
- Stimulation of glycogen synthesis and glucose oxidation in skeletal muscle
- Stimulation of glycogen synthesis in isolated hepatocytes



GIP, GLP-1 and diabetes

INSULINOTROPIC ACTION OF GIP AND GLP-1



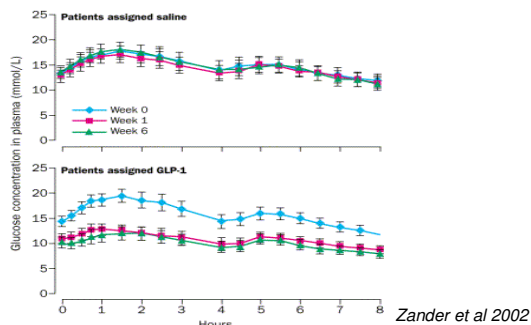
GIP AND GLP-1 IN THE AETIOLOGY OF DIABETES

- GIP action diminished in type 2 diabetes
- ? Reduced B-cell GIP receptor levels?
Reduced levels in animal models of diabetes (Vancouver diabetic Zucker rat)
- GLP-1 activity preserved in type 2 diabetes

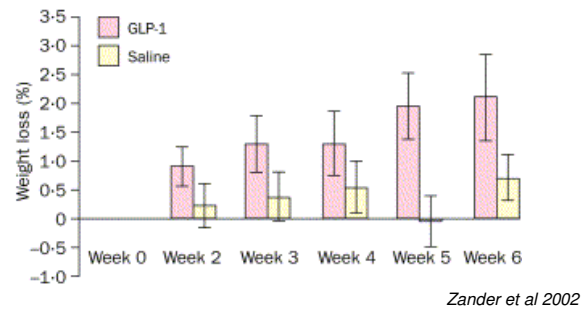
GLP-1 IN THE TREATMENT OF DIABETES?

- Increased GLP-1 sensitivity in GIP receptor k/o mice
- GLP-1 stimulates insulin gene expression
- GLP-1 has growth-hormone like effects on B cells
- GLP-1 inhibits apoptosis in B cells
- GLP-1 delays gastric emptying
- GLP-1 inhibits glucagon secretion
- GLP-1 exerts insulin-like effects on peripheral tissue
- GLP-1 promotes satiety (decreases appetite)

EFFECT OF 6-WEEK CONTINUOUS INFUSION OF GLP-1 ON GLUCOSE TOLERANCE IN TYPE 2 DIABETICS

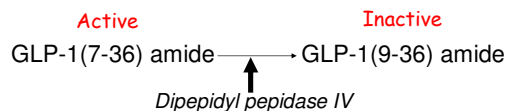


EFFECT OF 6-WEEK CONTINUOUS INFUSION OF GLP-1 ON BODY WEIGHT IN TYPE 2 DIABETICS



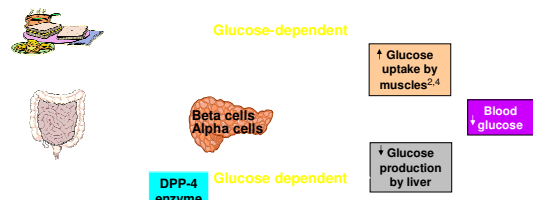
A major problem....

- Short plasma half life – not suitable for subcutaneous injection



- Solution:
- ✓ Inhibit DPPIV
 - ✓ Synthesise DPPIV-resistant analogues
 - ✓ Naturally occurring GLP-1 analogues (eg exendin-4) with longer half-life

Role of Incretins in Glucose Homeostasis



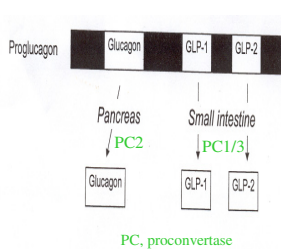
History of Incretins

- Concept proposed in 1906 by Moore; secretin proposed as gut hormone that enhanced postprandial insulin release
- Term incretin introduced 1932 by LaBerge
- Berson and Yalow developed RIA for insulin in 1960s, after which several groups found plasma insulin levels were higher after PO than IV glucose when BG was the same
- Term entero-insular axis coined by Unger (1969)
- GIP isolated by Brown in 1969 (Gastric Inhibitory Peptide)
- GLP-1 (7-36) discovered in 1988 (Göke)
- Term incretins (glucoincretins, insulinotrophic hormones) today refer to hormones/peptides that reduce glucose excursions into blood after a meal via various mechanisms

GIP as an incretin

- Glucose-dependent Insulin-releasing Peptide
- 42 aa peptide; $t_{1/2}$ 7-8 min
- Made in intestinal K cells
- Released by carbs and fat
- GIP-RA GIP_{7-30} reduces postprandial insulin in rats (pro-diabetic)
- GIP-R gene deletion leads to glucose intolerance and impaired insulin secretion in mice

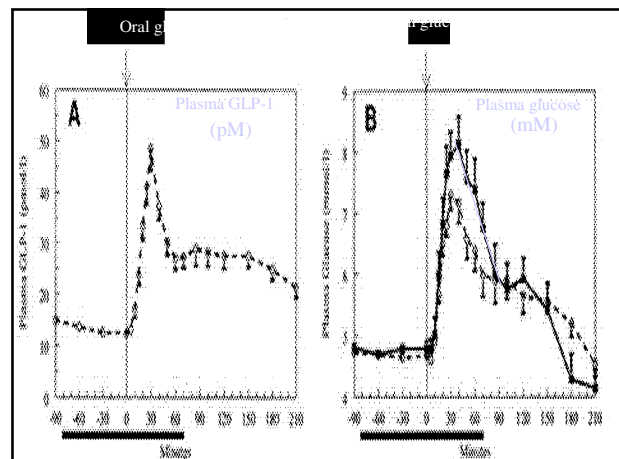
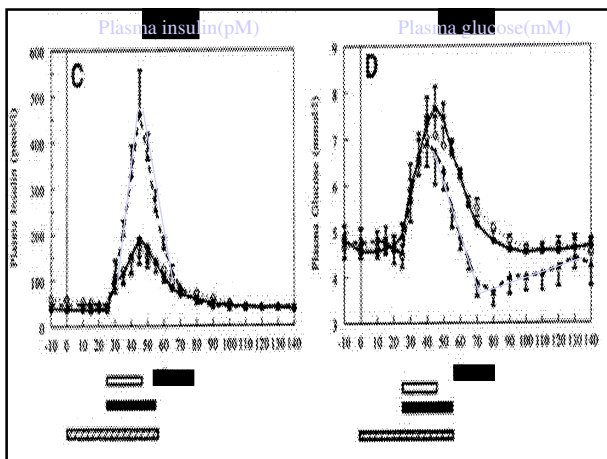
GLP-1 as an incretin



- Glucagon-Like Peptide-1
- 30 aa peptide; $t_{1/2}$ 1-2 min
- Made in intestinal L cells by action of proconvertase 1 and 3 on proglucagon
- Released by carbohydrates
- GLP1-RA exendin $9-39$ amide reduces postprandial insulin secretion in humans (pro-diabetic)
- GLP-1 gene deletion leads to glucose intolerance and impaired insulin secretion in mice

Physiology of the incretin, GLP-1

- Rapid release from ileal L cells within 15 minutes of eating (neural / ? GRP)
- Releases insulin if BG is $>70-90$ mg/dL via GLP-1R, adenylate cyclase, cAMP, PKA
 - Therefore little risk of hypoglycemia with GLP-1 Rx
- Increases insulin gene transcription, leads to β cell proliferation, and \downarrow β cell apoptosis
- Rapid metabolism in blood by dipeptidyl peptidase IV (DPPIV), or CD26 to inactive fragment GLP-1_{3-30}



Effects of GLP-1 and GIP on Glucose Metabolism

GLP-1

- ↑ insulin (incretin)
- ? insulinomimetic
- ↑ islet/β cell mass
- ↓ glucagon secretion and hepatic gluconeogenesis
- ↓ gastric emptying

GIP

- ↑ insulin (incretin)
- insulinomimetic
- ↑ islet/β cell mass
- ↑ glucagon secretion but ↓ gluconeogenic response to glucagon
- ↓ gastric emptying

GLP-1, Glucagon, and Satiety

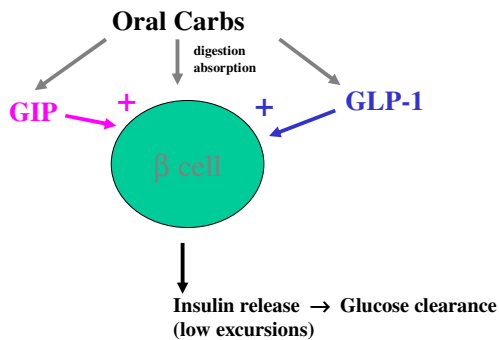
GLUCAGON

- GLP-1 ↓ glucagon sec'n
 - Indirect, via ↑ insulin and somatostatin
 - Direct, via GLP-1R on α cell
- High I/G ratio ↓'s hepatic glucose production
- Possible role in type 2 DM
 - ↑ serum glucagon in type 2
 - ↓ glucose suppression of glucagon release in type 2 DM

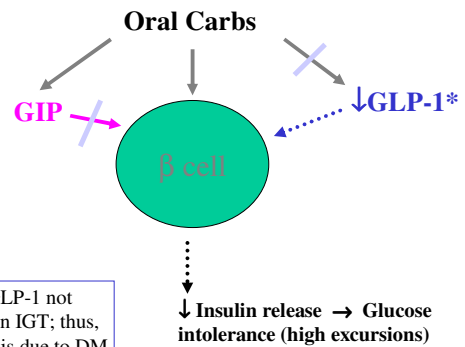
SATIETY/GASTRIC EMPTYING

- GLP-1 infusion results in early satiety
- GLP-1Rs exist in the hypothalamus (satiety center)
- GLP-1 slows gastric emptying (ileal "brake") which can contribute to satiety

NORMAL GLUCOSE TOLERANCE

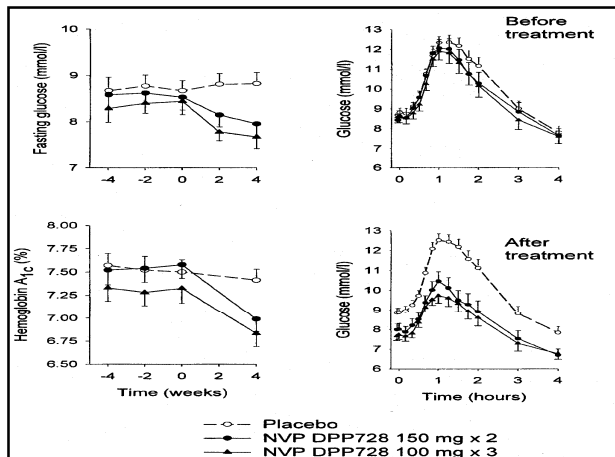


TYPE 2 DIABETES MELLITUS



Antidiabetogenic role of GLP-1

- Glucose analog 1,5-anhydro-D-fructose enhances endogenous GLP-1 release (no trials in humans as yet; animal studies promising)
- Continuous subcutaneous infusion of GLP-1 for 6 weeks ↓ FPG 80 mg% and hemoglobin A_{1c} by 1.3% in type 2 DM
- GLP-1 receptor agonist peptides that are resistant to DPPIV:
 - NN2211 (lyraglutide), sq once/day ↓ FPG from 146 to 124 mg/dL
 - Exendin-4 (from venom of Gila monster, with 50% homology to GLP-1) subcut. bid ↓ A_{1c} from 9.1 to 8.3% after 1 month
- Inhibition of DPPIV by oral NVP DPP728:
 - ↓ FPG and PP-BG by around 1 mmol/L (18 mg/dL) in mild type 2 DM on no oral agents after 4 weeks, with ↓ in A_{1c} from 7.4% to 6.9% and minimal side effects so far



Conclusions

- Glucose intolerance better predicts macrovascular disease outcomes than does fasting glucose
- Glucose tolerance can be improved with α -glucosidase inhibition, with reduced macrovascular complications and primary prevention of hypertension
- Glucose intolerance may in part be due to reduced incretin release and/or action (GLP-1, GIP, others)
- GLP-1 agonists or inhibitors of GLP-1 degradation may benefit patients with type 2 (or type 1) DM
- Other incretins such as GIP may also be of benefit

	Hypoglycemia	Wt. Gain	Edema	GI effects	Lactic Acidosis	Liver Toxicity	Use in Renal Failure
Glyburide	4+	+	0	±	0	±	-
Gliclazide	2+	+	0	±	0	±	+
Glimepiride	2+	+	0	±	0	±	+
Repaglinide	1+	+	0	0	0	0	+
Nateglinide	1+	?	0	0	0	0	+
Metformin	0	0	0	2+	+	0	-
Acarbose	0	0	0	3+	0	±	±
Rosiglitazone	0	+	+	0	0	±*	+
Pioglitazone	0	+	+	0	0	±*	+

* Liver enzyme monitoring recommended in product monographs
Adapted from Lebovitz H: Endocrinol & Metab Clinics of NA; 30 (4)909-933