TOSS1-2: Glucose Homeostasis

Glucose Homeo = begins @ oral cavity already (saliva = Amylase)

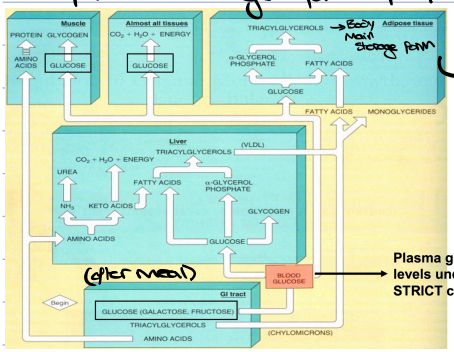
small intestine: pancreatic juice (amylase)
: Intestinal secretions: Sucrase
↳ Absorption (via 2° Active transport) : Maltase
↳ symport : Lactase

Glucose = 1° E⁻ substrate
↳ Brain & NS (Especially)

Brain & RBC only use Glucose

Brain uses ketones in Absolute Glucose shortage

Body Main Storage form of Glucose = TG formation! { 1 Glycerol, 3 Fatty A.

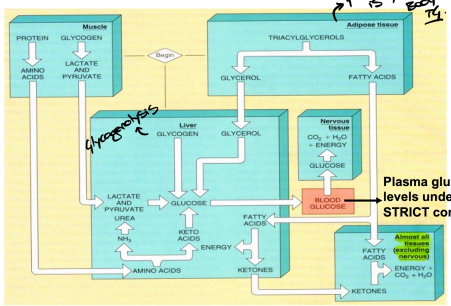


Plasma glucose levels under STRICT control!!

↳ if Glycogenolysis & Gluconeogenesis is ↓ enough then Body mobilizes TG.

THEME 3, Sessions 1-2

GLUCOSE HOMEOSTASIS: FASTING SITUATION



Plasma glucose levels under STRICT control!!

ultimate purpose of eating = cellular Metabolism

Glucose yield less ATP than Lipids but is more efficient

Glucose → ATP (3 processes)
1) Glycolysis
2) CAC (Citric A. cycle)
3) Gluconeogenesis → Lipolysis
→ Amino A.

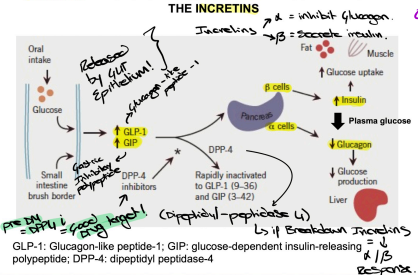
Endocrine Response to carb containing Meal:

Eating Meal { ↑ Blood Glucose → Insulin Secretion
Stretch R. of GIT → CNS → Pancreas

↳ Ingestion = Incretin Release
↳ GIP
↳ GLP-1
} ↑ Insulin Response

almost like a pre-response (knows Glucose CJ ↑ ∴ pre-emptively release Glucose).

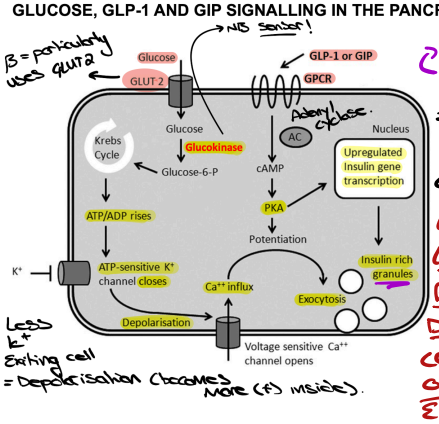
ENDOCRINE RESPONSE TO CARBOHYDRATE-CONTAINING MEAL: THE INCRETINS



GLP-1: Glucagon-like peptide-1; GIP: glucose-dependent insulin-releasing polypeptide; DPP-4: dipeptidyl peptidase-4

β-cell

GLUCOSE, GLP-1 AND GIP SIGNALLING IN THE PANCREATIC β-CELL:



↑ insulin transcrip
GLP-1 / GIP
= GPCR ↓ potentiates Ca^{2+} influx
GLUT2
Glucokinase
ATP-sen. K^+ Depolar
Ca^{2+} channel open
Exocytosis.

Cellular Actions of Insulin:

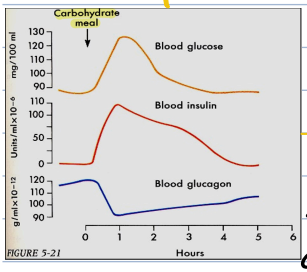
Insulin R.: tetramer protein (2α / 2β)
↳ tyrosine-kinase R. (2x Binding sites) (transmembrane)
↳ PI_3-kinase-protein kinase B/AKt pathway
=> Liver, Muscle, Adipocytes all have R.
Tyrosine Amino A. = phosphorylated in β-cell.
↳ NB since R. = Dimer = need 2 insulin Mol. bind simultaneously for tyrosine kinase to work.

Main control of Plasma Glucose:

→ Insulin (↓ plasma Glu)
→ secreted in opp conditions.
→ Glucagon (↑ plasma Glu)
→ Fx are opp. ↳ Glycogenesis / protein syn / lipogenesis

FED state → Insulin Dominant (↓ Blood Glu) [Store]

FASTING state → Glucagon Dominant (↑ Blood Glu) [Mobilize]
↳ Glycogenolysis
↳ Gluconeogenesis



Islets of Langerhans

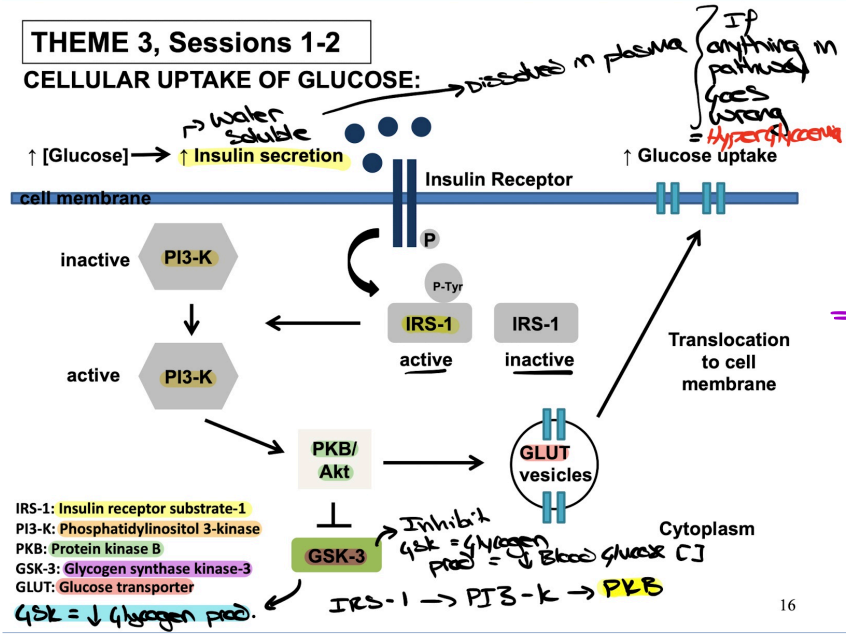
α cells = Glucagon
β cells = Insulin
δ cells = Somatostatin

only 1-2% of pancreas cells are endocrine (mostly in tail of pancreas)

Cellular uptake of Glucose

THEME 3, Sessions 1-2

CELLULAR UPTAKE OF GLUCOSE:



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GLUT-2 = pancreas | GLUT4 = Liver/fat/muscle

↳ Insulin → R. → IRS-1 → PI3-k → PKB/Akt
↳ IRS-1 (p-tyr)

NB points

1) Insulin = H2O soluble.
2) Tyrosine kinase phosphorylates IRS-1 (Insulin R. substrate 1)
3) IRS-1 activates PI_3-k
4) PI_3-k activates PKB
5) PKB ⊣ GSK (Glycogen synthase kinase 3)

⇒ GSK-3 ⊣ Glycogen synthase

∴ by inhibiting GSK = ↑ Glycogen synthase act.
∴ ↑ CJ Glycogen ∴ ↓ Glucose CJ!!

NB if Anything in this pathway has an issue = Hyperglycaemia

∴ Insulin → uptake (↑ Glut 4's)
→ Glycogen prod! (⊣ GSK-3)

↑ GLUT4 (↑ uptake)

⊣ GSK-3 (↑ Glycogen prod)

Factors affecting insulin Release:

Stim:	Inhibitory
HyperGlycaemia	Somatostatin
Amino A.	NE } want to ↑
Long chain fatty A.	Epi } Blood Glucose.
GIT Hormones (Gastrin/Secretin)	
ACh	
Sulfonylureas	

insulin = PKB

Biological Fx of Insulin: Anabolic

GLUT4 = Glucose uptake
R. Binding = Activates synthesis pathways → Glycogen, TG, VLDL, Cholesterol, Protein
Insulin = super NB in Growth & Development
GH = IGF1 release

↳ ∴ GSK ⊣ GS

→ GSK phosphorylates GS
when phosphorylated GS = ⊖ Activity

→ want to ↑ prod of Glycogen.

PKB ⊖⊣ Glycogen synthase kinase
PKA ⊕↗ Glycogen synthase kinase

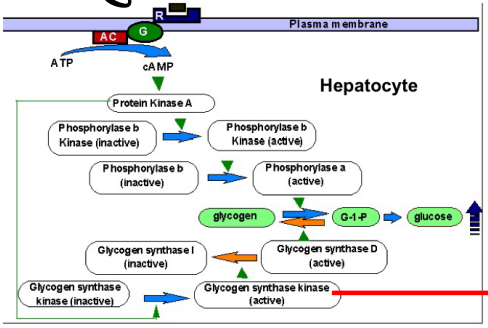
↳ want to breakdown Glycogen

↳ Glucagon = ↑ PkA.

Glucagon: REIN control pair (of insulin)

Glucagon = catabolic
peptide Hormone (Secretin family)
Intracellular vesicle storage (Exocytosis)
Mechanism Unknown
most NB stim for release (⊕ only one) = ↓ Blood Glucose

Glucagon = GPCR = Adenyl cyclase (ATP → cAMP → PkA).



Glucagon = want to ↑ Blood Glucose ∴ ↓ Glycogen synth.
↳ Glycogenolysis ↩

∴ Glucagon → 1) phosphorylase a (promote)
→ 2) GSK (promote)

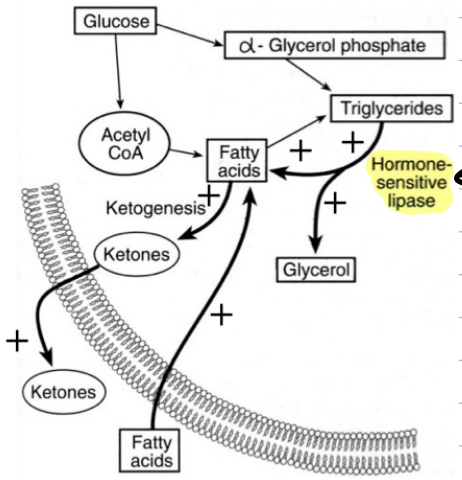
GSK = inhibits Glycogen Synthase
= promotes IRS-1 (p-ser) = IR. (IRS-1 Depletion)

∴ Inhibit GSK = ↑ Glycogen Synthase } GSK = Target for Rx.
= ↓ IR.

⇒ NB Glucagon = ketogenesis. → TG < Glycerol / FFA.
↳ Breakdown prod of fatty Acid.

↳ Brain = use ketones in absolute shortage of Glucose.
ketones = ↓ pH = Acidosis.

⇒ Lack of insulin = HSL ↑ (Hormone sensitive Lipase).



Factors that influence Glucagon Release:

(+):	(−):
Hypoglycaemia	fatty A.
Amino A.	somatostatin
ACh	Insulin.
NE	
Epi	

Biological fx of Glucagon:
cAMP phosphorylation = 1) Glycogenolysis (Liver)
2) Lipolysis (Adipose)
3) Gluconeogenesis (Liver)
4) ketogenesis (Liver)

↑ plasma Glucose.
↑ plasma FFA.
↑ plasma ketones.

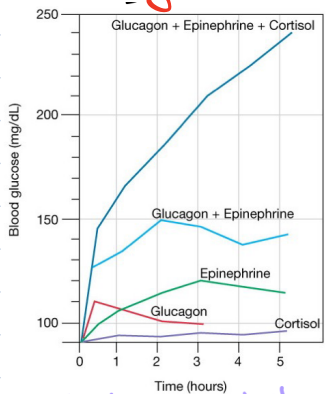
Terminology

Glycogenolysis: Glycogen → Glucose
Lipolysis: TG → Glycerol (+) FFA.
Glycolysis: Glucose → pyruvate
Gluconeogenesis: New glucose from non-carb precursors
Ketogenesis: Synth of ketones (from FFA.)

2 Hormones mitiate < Glucagon / cortisol.

Glycerol
Lactate
Amino A.
} occurs in Liver & kidney

Diabetogenic Effects → Hormones that ↑ Blood Glucose < Glucagon / Epi / cortisol.



cortisol ∅ very potent as a diabetogenic hormone.
Glucagon = potent short term
Epi = potent & max @ 3h mark.

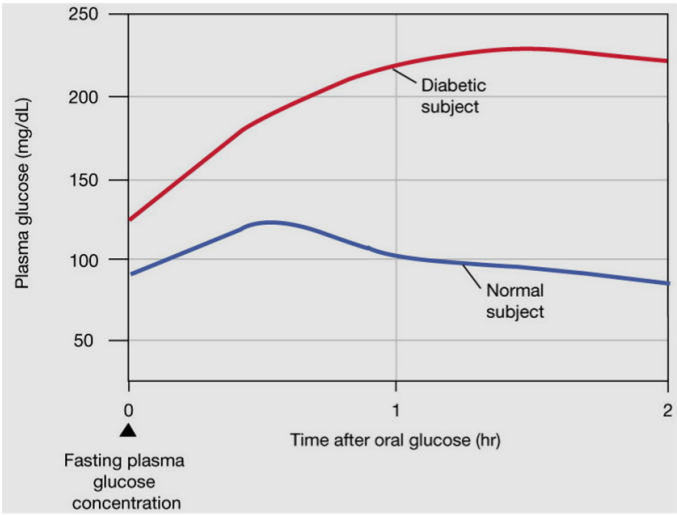
NB → Muscles = ∅ share its Glucose from Glucagon (Liver does though)
↳ proteinolysis = last resort

DM pathophysiology → occurs when insulin loss Ability to control regulate Blood Glucose levels.

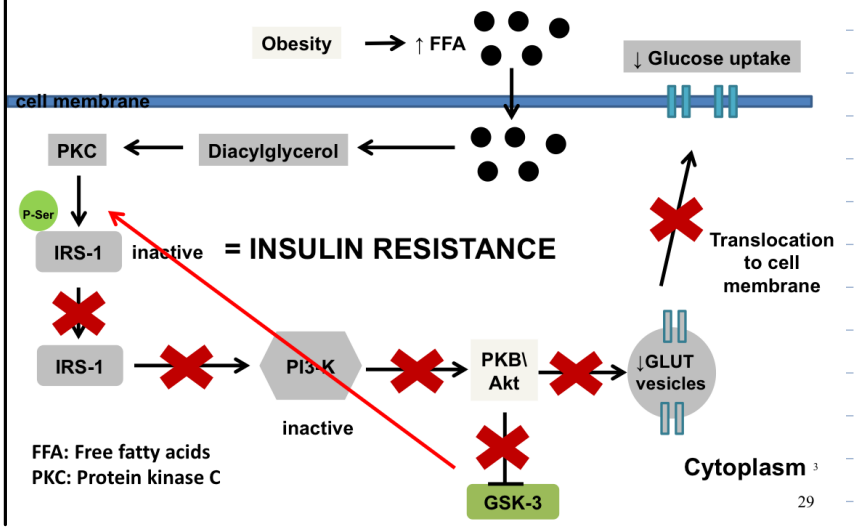
Either ↓ insulin [] (pancreatic issue)
↓ insulin Action (IR) → problem in pathway.
} = ↓ Glucose uptake (muscle/fat/liver) ∴ ↑ Glucose plasma []

Glucose tolerance test → ultimate Dx of DM.

GLUCOSE TOLERANCE TEST:



INSULIN RESISTANCE:



obesity = ↑ FFA
= FFA induce PKC via Diacylglycerol

normal IRS-1 activation = p-tyr. (PKB)
PKC = IRS-1 (p-ser) → inactivates IRS-1

Normal pathway Halts (IRS-1 ↓)

↳ NB GSK now also ø being inhibited ∴ Glycogen ø formed (PKB inhibits GSK).
∴ GSK i = GS↑
ø GSK i = GS↓
} ∴ ↑ Glucose [] drastically = Hyperglycaemia.

[↑GSK = ↓ GS]

GSK = also provokes PKC ∴ ↑ IRS-1 (p-ser) = Loop!

if develop GSK i = ↑ Glycogen (↓ Blood Glu)
= ↓ IRS-1 (p-ser).
} GSK = Good target

ø GSK = ↑ Glycogen prod.