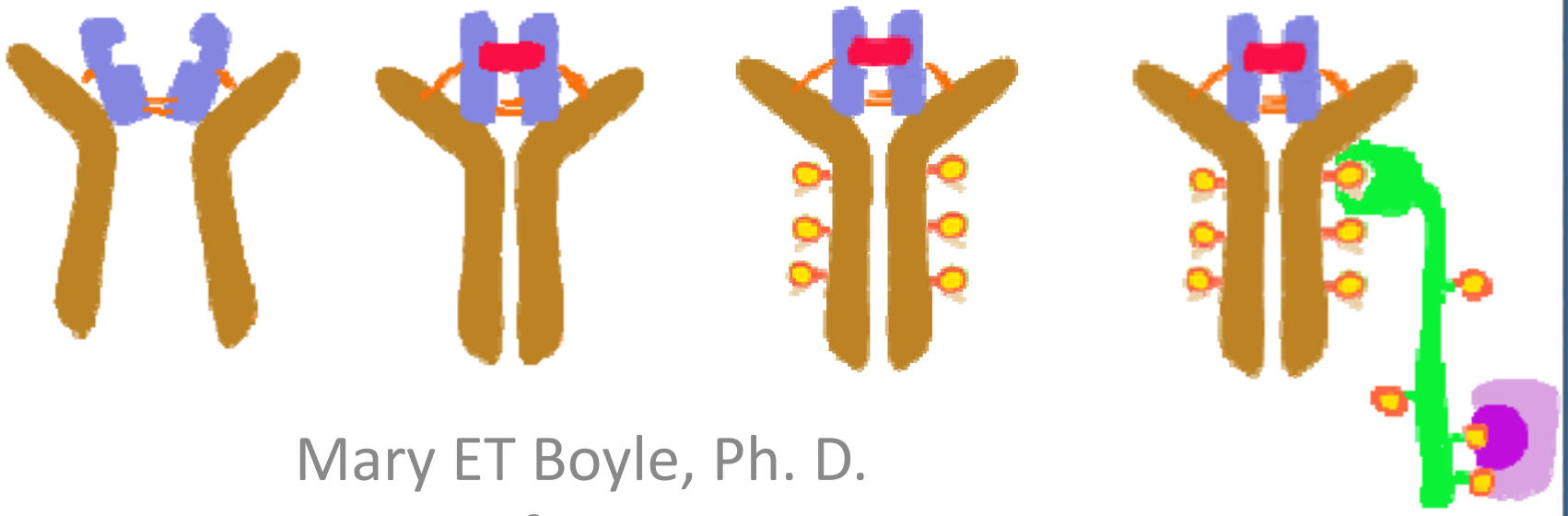
Insulin receptor and signaling



Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD

Hormones receptors are discriminating!

Hormones are present at very low concentrations

(atto- to nanomolar range

10^{-15} to 10^{-9} mol/L)

The concentration is much lower than many structurally similar molecules (sterols, aa, peptides, proteins) circulating

(micro to millimolar 10^{-6} to 10^{-3} mol/L) range

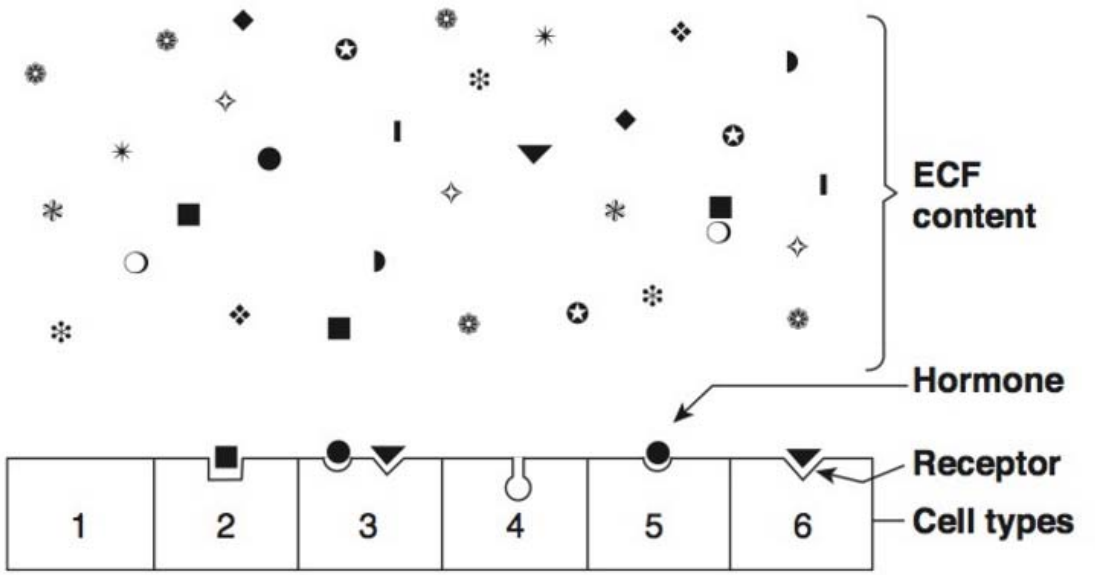
Terminate the effect of a hormone?

Usually when the hormone disassociates from the receptor (but not always)

Target cells must distinguish between different hormones and other molecules that have a much higher concentration

Hormones initiate their effects by binding to specific receptors

Specificity and Selectivity of Hormone Receptors



Features for effective hormone-receptor interactions:

1. Binding should be specific
2. Binding should be saturable
3. Binding should occur within the concentration range of the expected biologic response

Regulation of Glucose Homeostasis

Insulin and leptin – info on long term energy supplies

Short term energy availability is conveyed by glucose and free fatty acids (FFA)

Food intake vs. reduced energy expenditure

Nutrient availability (increased endogenous glucose production) vs. excess energy storage – promote negative energy balance and limit endogenous glucose production.

Acute elevation of plasma glucose

Cognitive functions

Impaired neural function

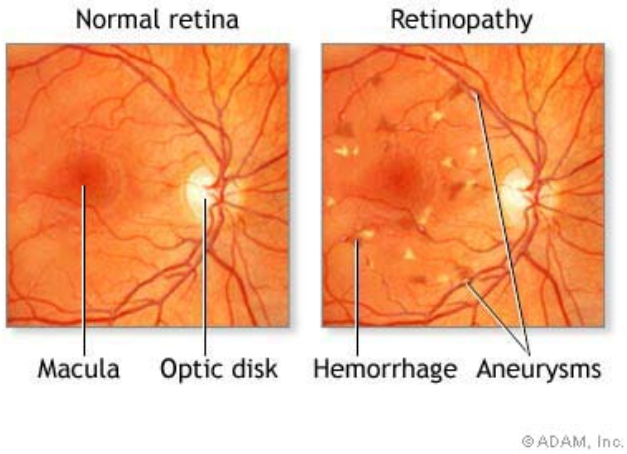
Damage of proteins causes diabetic complications:

neuropathy

nephropathy

retinopathy

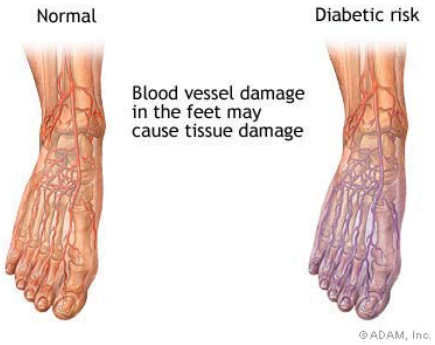
Microvascular complications



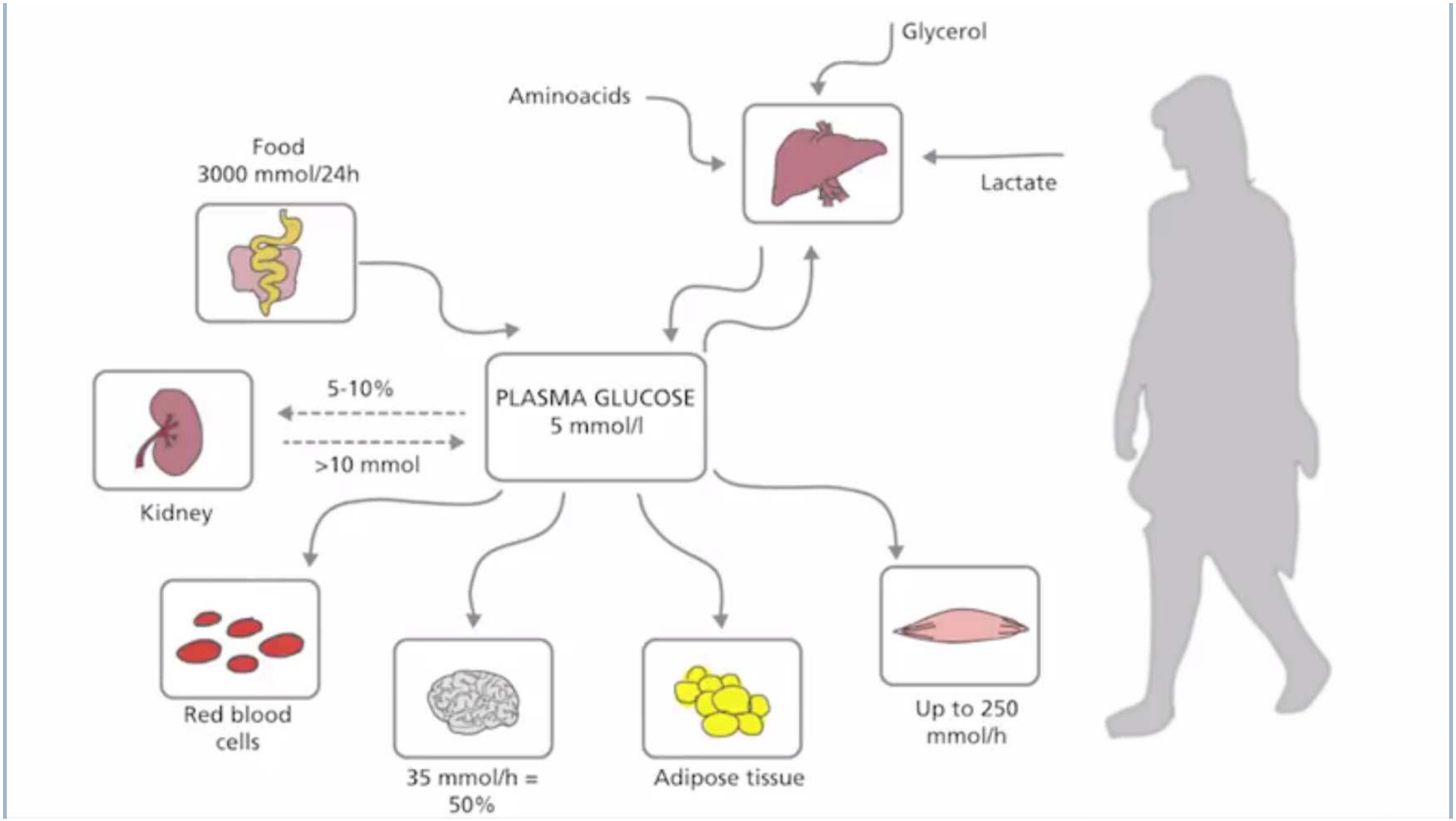
Elevation of plasma glucose

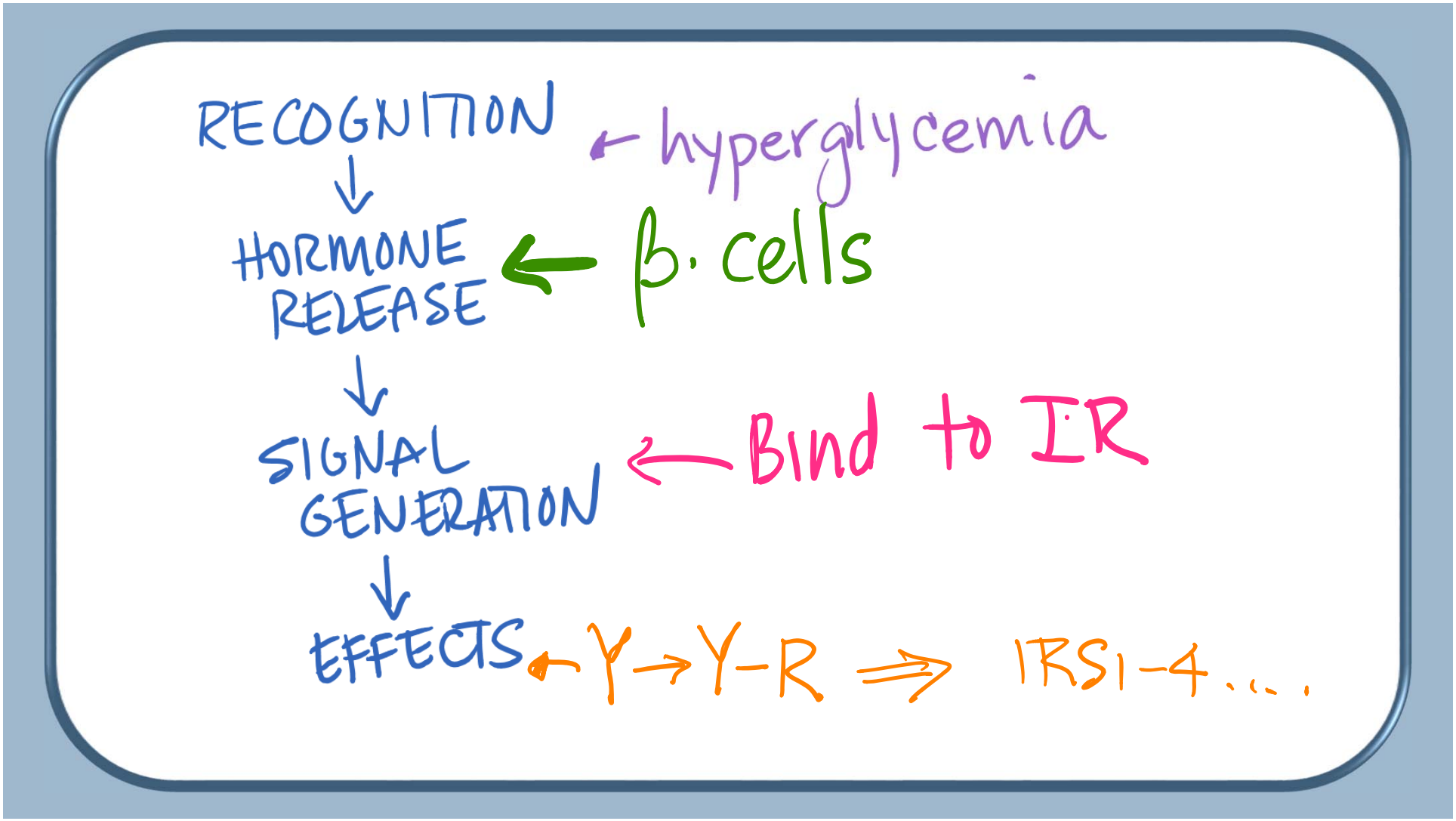
Chronic hyperglycaemia

- Myocardial infarction
- Stroke
- Amputations



Macrovascular complications


Glycerol
Aminoacids
Lactate
Food
3000 mmol/24h
5-10%
>10 mmol
PLASMA GLUCOSE
5 mmol/l
Kidney
Red blood
cells
35 mmol/h =
50%
Adipose tissue
Up to 250
mmol/h


RECOGNITION
hyperglycemia
HORMONE RELEASE
β-cells
SIGNAL GENERATION
Bind to IR
EFFECTS
Y → Y-R ⇒ IRS1-4....

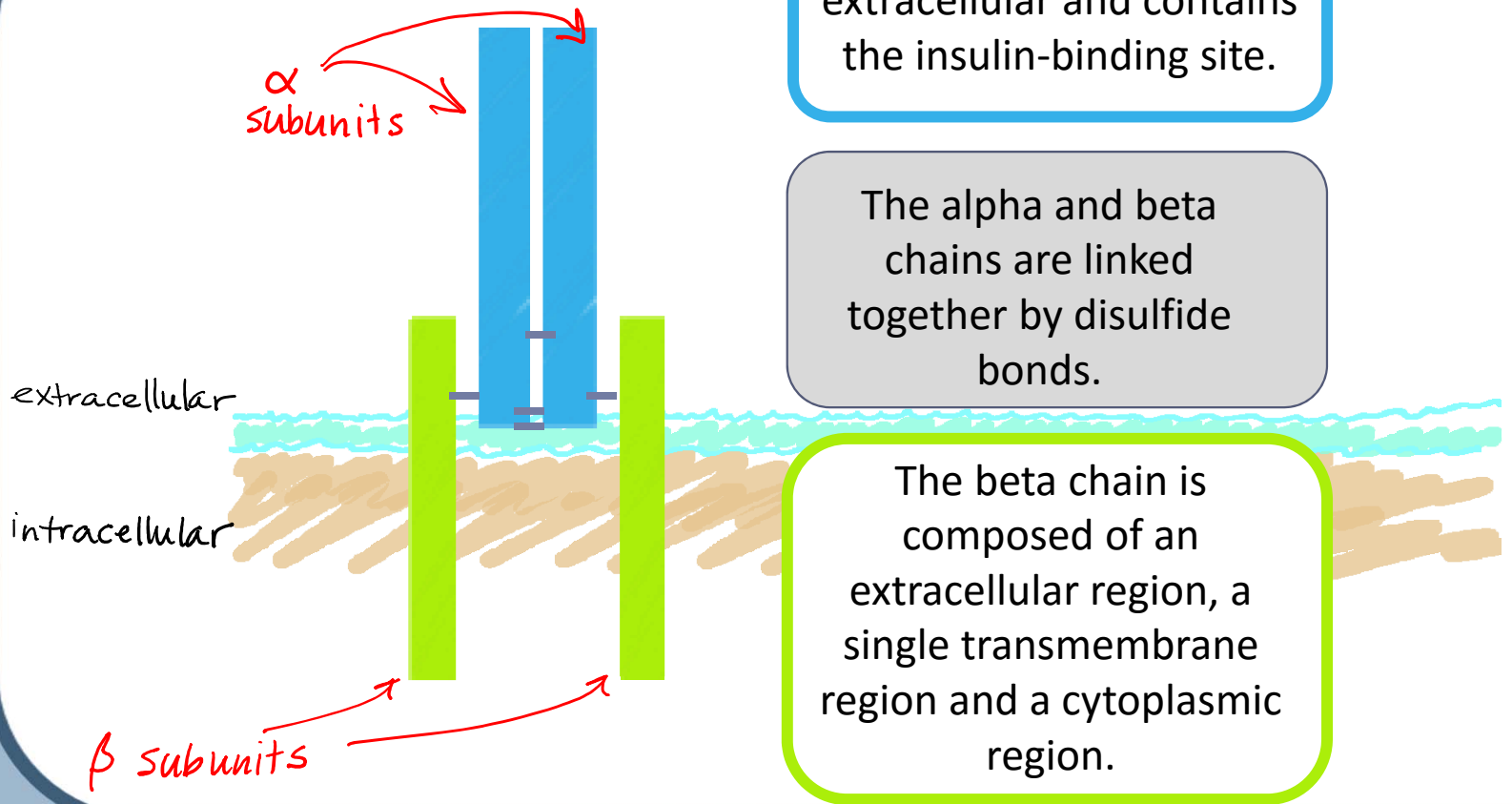
Insulin receptor is:

The effector of insulin action

A member of the tyrosine kinase receptor family

Insulin has effects on CNS

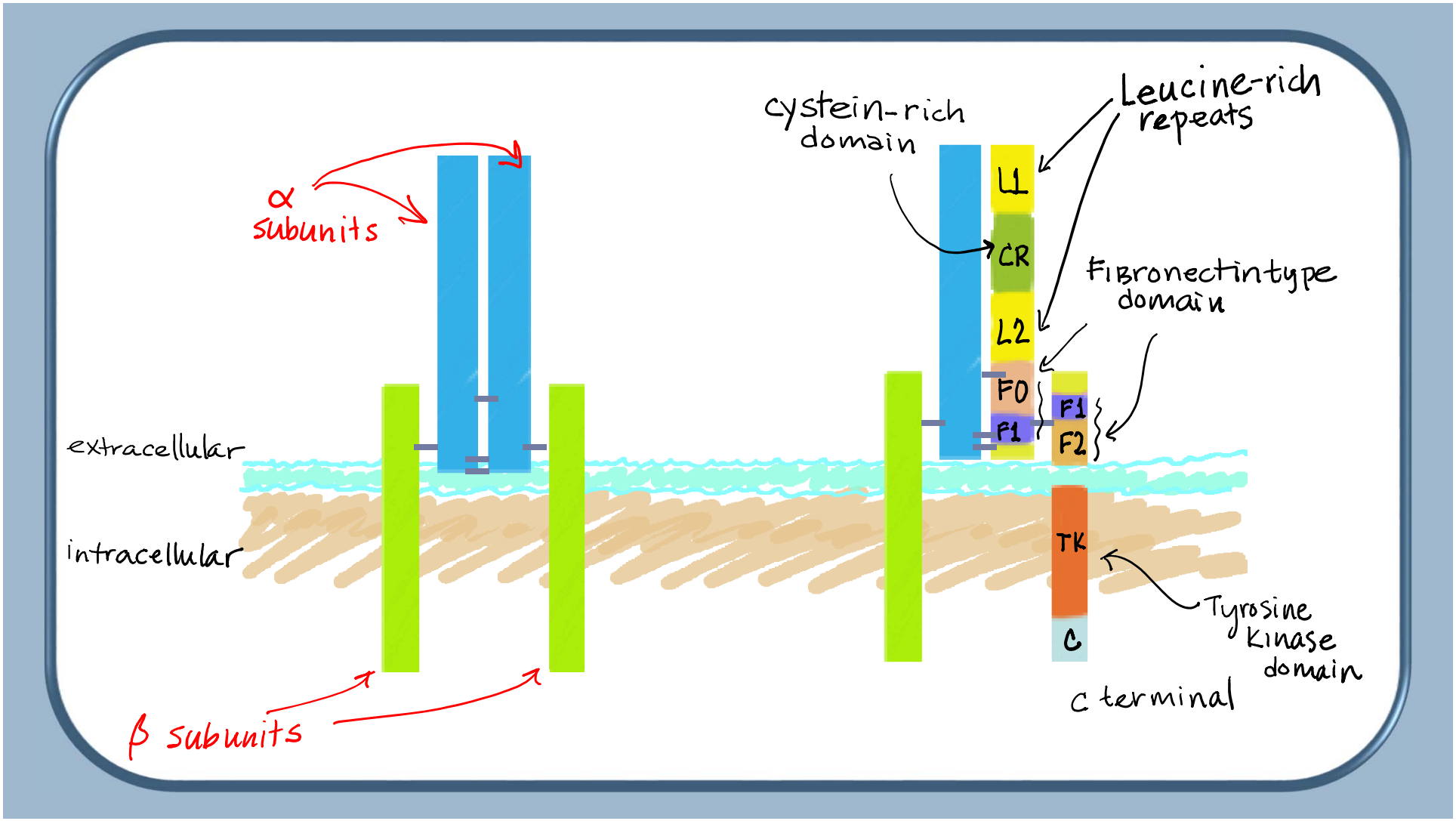
Regulation of energy homeostasis, reproductive endocrinology and neuronal survival.

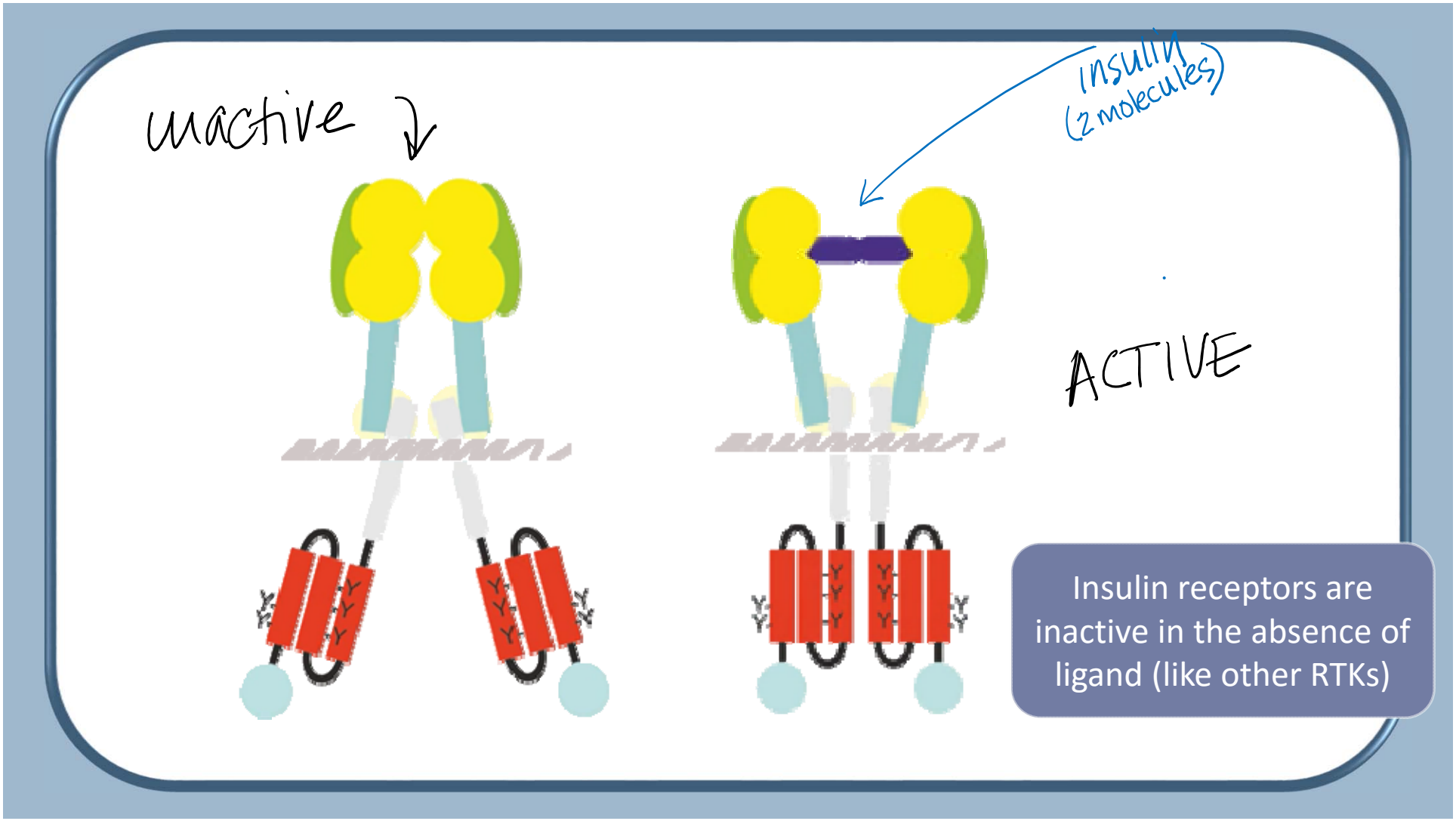


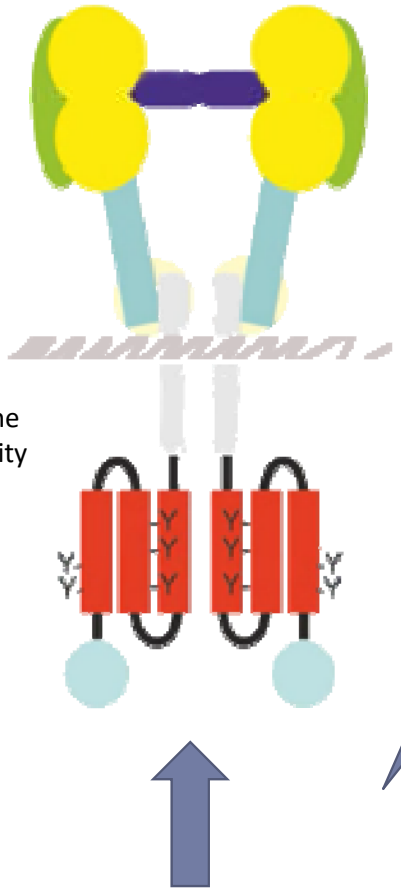
The alpha chain is entirely extracellular and contains the insulin-binding site.

The alpha and beta chains are linked together by disulfide bonds.

The beta chain is composed of an extracellular region, a single transmembrane region and a cytoplasmic region.


α subunits
β subunits
extracellular
intracellular
cystein-rich domain
Leucine-rich repeats
L1
CR
L2
Fibronectin type domain
F0
F1
F1
F2
TK
C
Tyrosine kinase domain
c terminal


inactive
insulin
(2 molecules)
ACTIVE
Insulin receptors are inactive in the absence of ligand (like other RTKs)



Low tyrosine kinase activity

When insulin binds, there is a conformational change and the tyrosine kinase domains come into close physical proximity.

Juxtaposition of the kinase domains leads to trans-autophosphorylation and receptor activation.

There are three phosphorylation sites present in the activation loop.

In the unphosphorylated state, the activation loop assumes a conformation in which it occupies these sites.

Upon phosphorylation of the three tyrosine residues

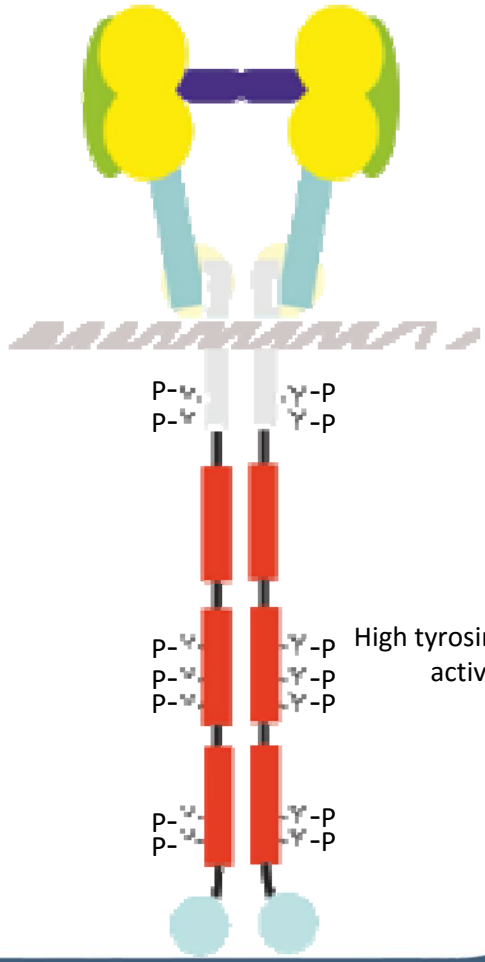
the activation loop assumes a new conformation away from the catalytic cleft

the activation loop assumes a new conformation away from the catalytic cleft

This confirmation requires a rotation of the small and large lobes of the kinase domain with respect to each other, thereby bringing residues that are essential for catalysis closer together.

the activation loop now leaves the catalytic cleft open so that it can bind substrates.

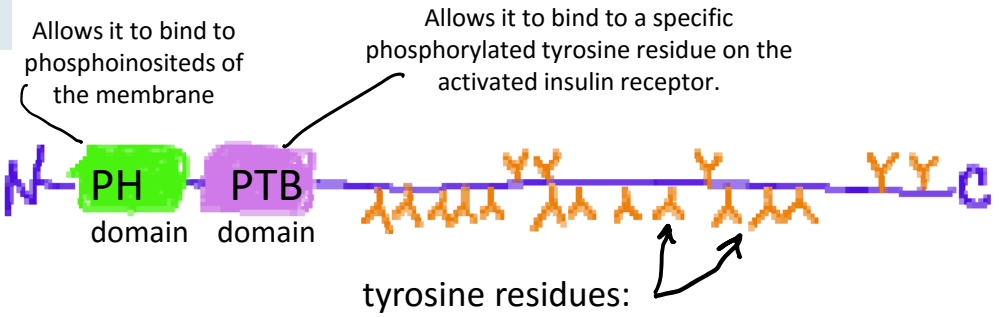
Following activation of the kinase domain, the receptor phosphorylates itself on tyrosine residues that are present adjacent to the membrane and in the carboxyl-terminal tail.

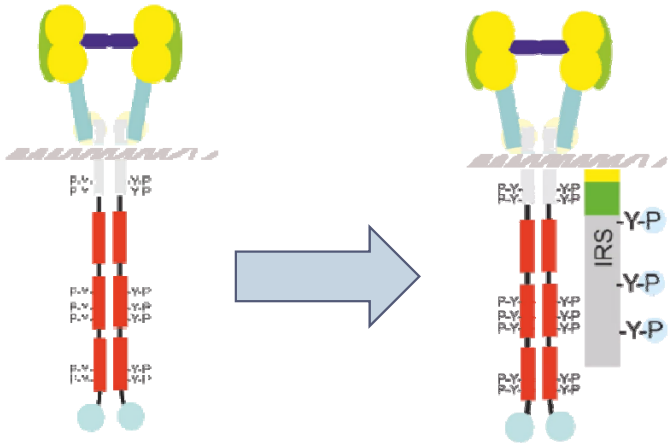


Tyrosine-phosphorylated IRS activates signaling pathways

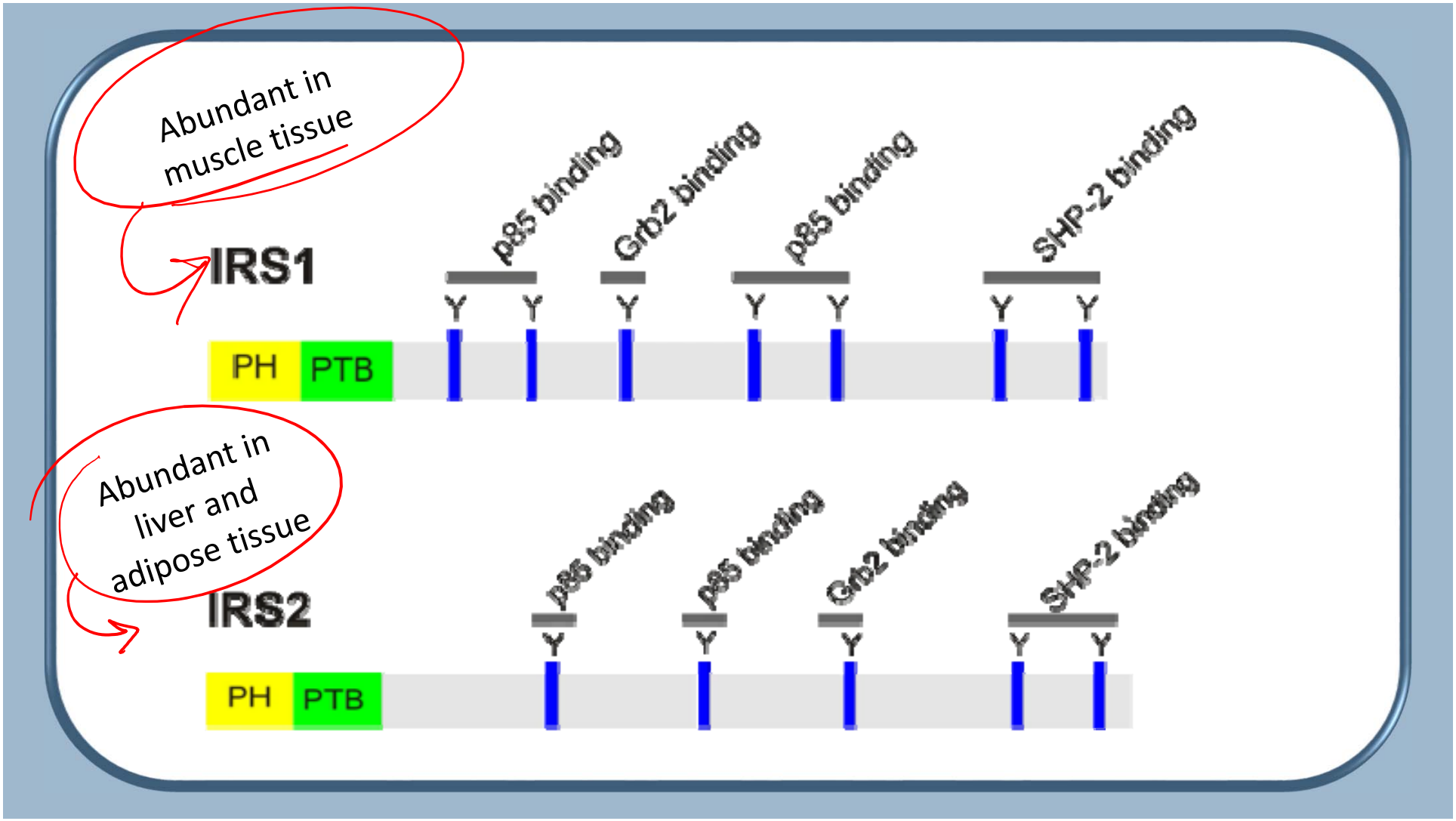
(IRS: insulin-receptor substrates)

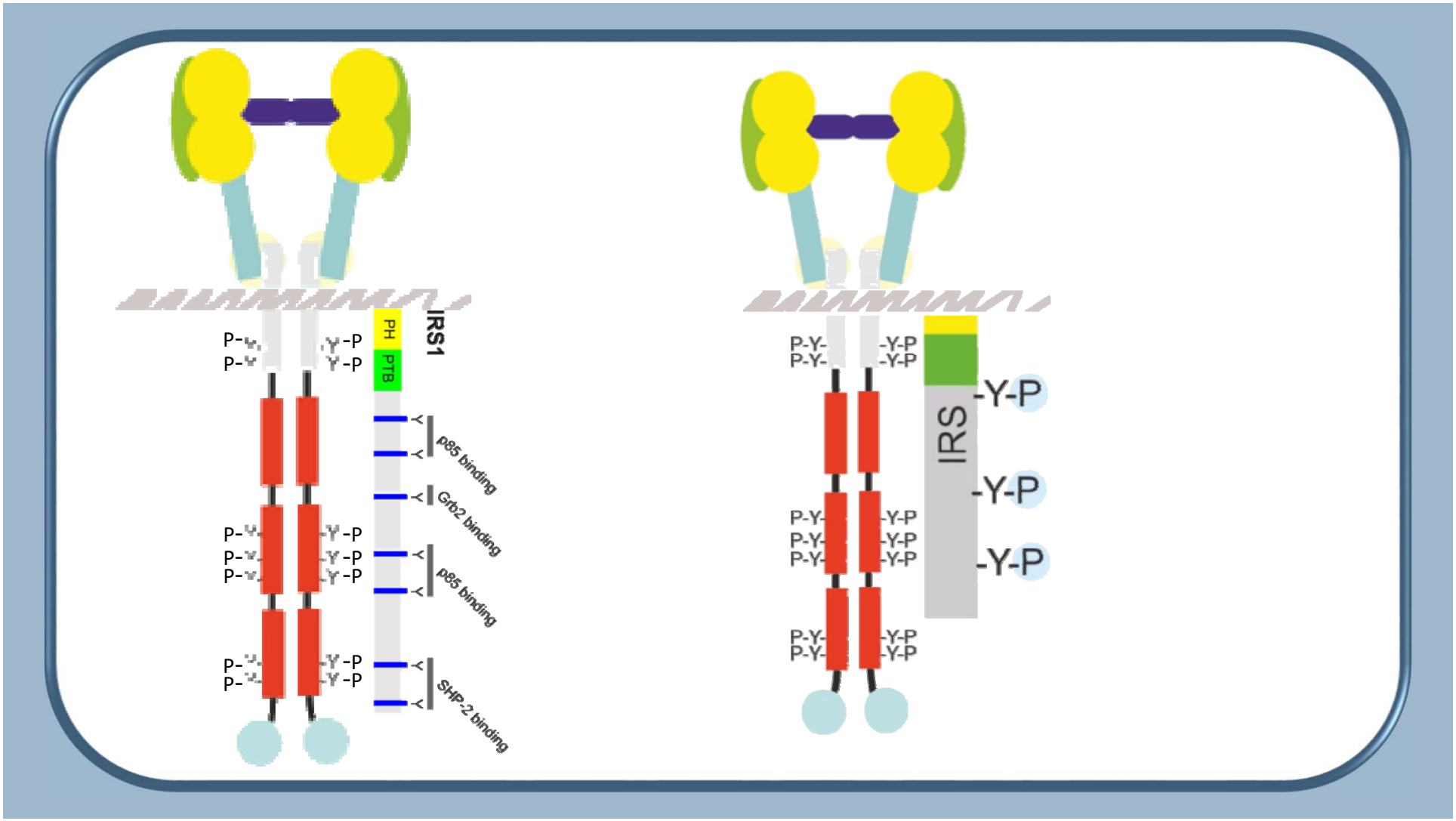
A schematic representation of an IRS polypeptide:

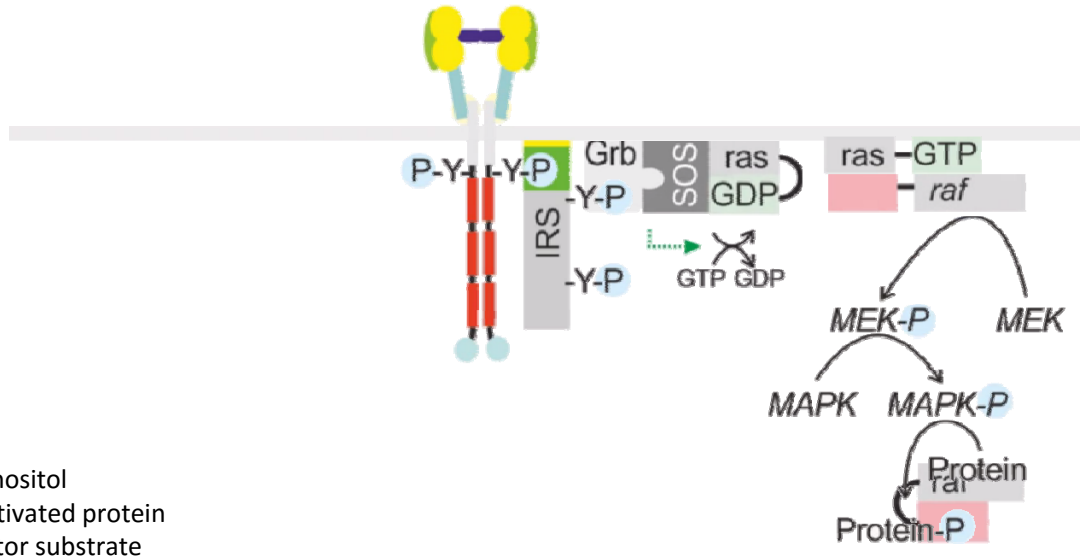




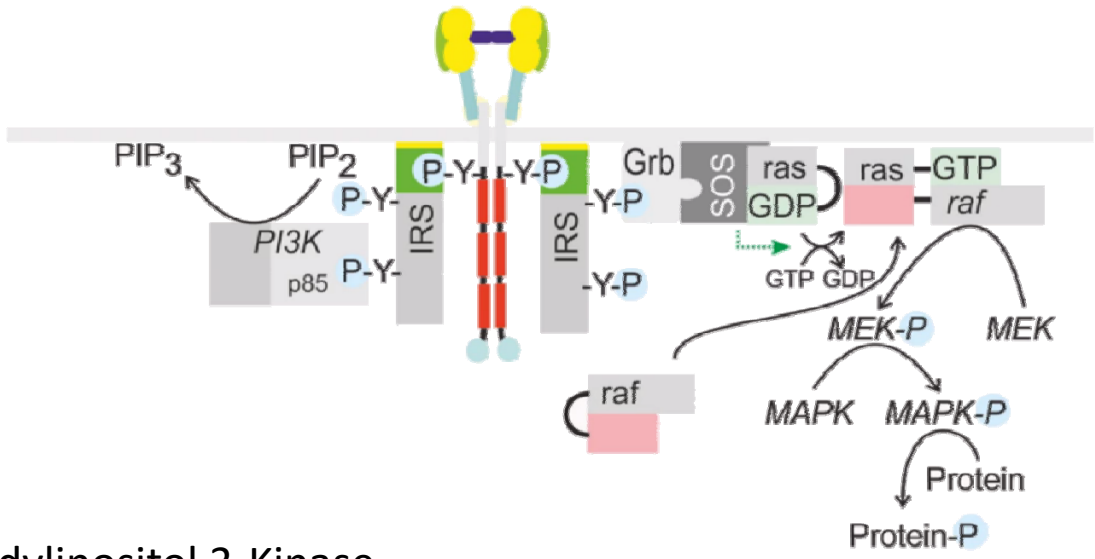
The insulin receptor associates with a small family of docking proteins, called insulin-receptor substrates (IRSs) which provide binding sites for SH2 domain-containing signaling proteins


Abundant in muscle tissue
IRS1
p85 binding
Grb2 binding
p85 binding
SHP-2 binding
Y
PH
PTB
Abundant in liver and adipose tissue
IRS2
p85 binding
p85 binding
Grb2 binding
SHP-2 binding
Y
PH
PTB


IRS1
PH
PTB
p85 binding
Grb2 binding
p85 binding
SHP-2 binding
IRS
-Y-P
-Y-P
-Y-P



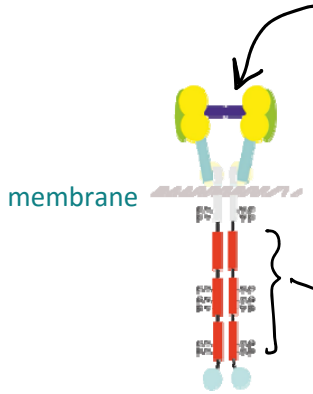
PI: phosphatidylinositol
MAP: mitogen activated protein
IRS: insulin receptor substrate
Grb: growth factor receptor bound protein



PI3K-phosphatidylinositol 3-Kinase

PIP_3 -phosphatidylinositol (3,4,5)-trisphosphate

Insulin signaling cascade



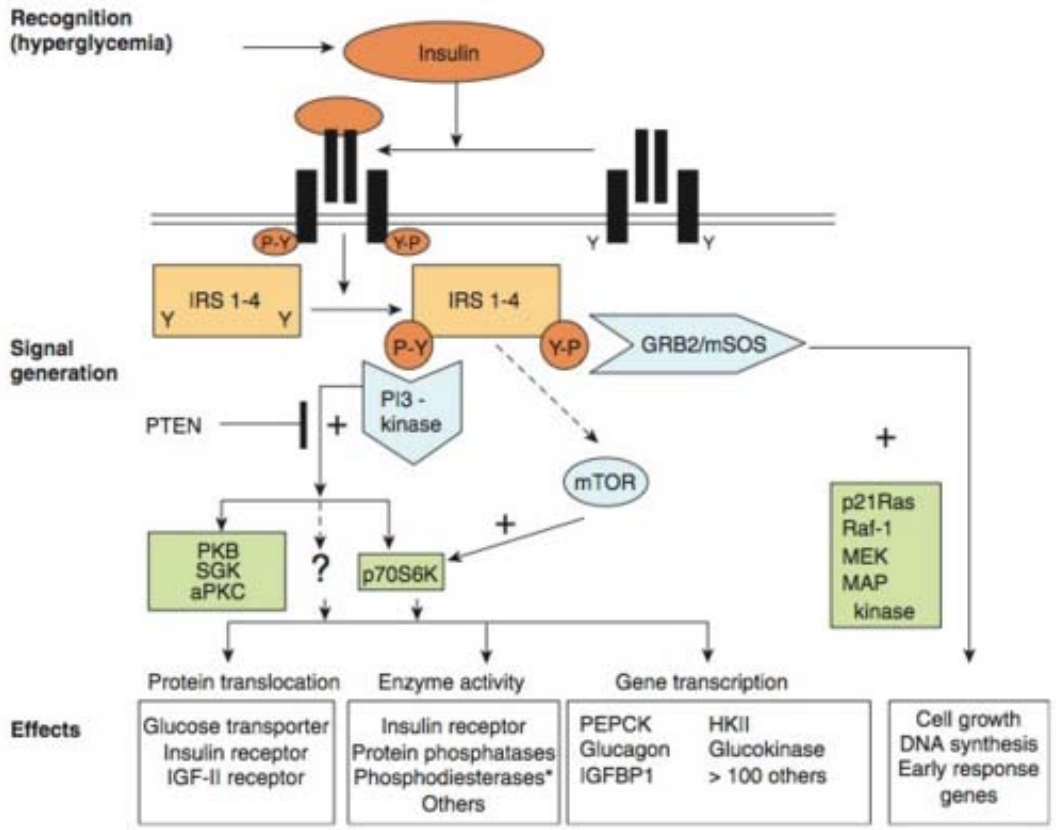
insulin receptor

PI: phosphatidylinositol
MAP: mitogen activated protein
IRS: insulin receptor substrate

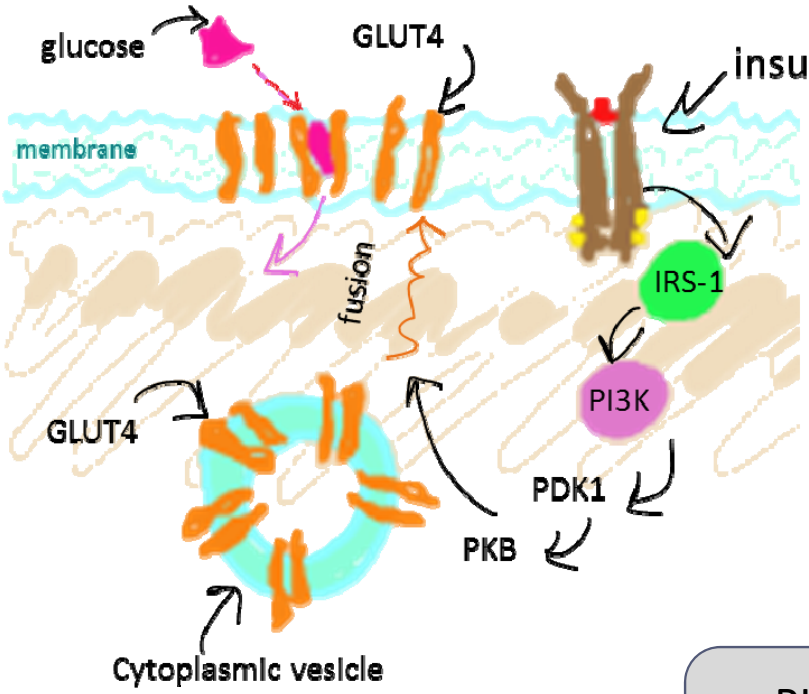
Phosphorylation of docking proteins
(IRS1-4, Shc, Gab-1)

Activation of signaling pathways
(PI3 kinase, MAP kinase)

Glucose transport | Glycogen synthesis | Lipogenesis Lipolysis | Protein synthesis | Gene expression | Cellular growth


Recognition
(hyperglycemia)
Insulin
P-Y
Y-P
Y
Y
IRS 1-4
Y
Y
IRS 1-4
P-Y
Y-P
GRB2/mSOS
Signal
generation
PI3 -
kinase
PTEN
+
mTOR
+
p21Ras
Raf-1
MEK
MAP
kinase
PKB
SGK
aPKC
?
p70S6K
+
Protein translocation
Enzyme activity
Gene transcription
Effects
Glucose transporter
Insulin receptor
IGF-II receptor
Insulin receptor
Protein phosphatases
Phosphodiesterases*
Others
PEPCK
Glucagon
IGFBP1
HKII
Glucokinase
> 100 others
Cell growth
DNA synthesis
Early response
genes

PKB regulates glucose transport: GLUT4



Glucose transporters (GLUT4) are stored in the walls of cytoplasmic vesicles that form by budding from the plasma membrane (endocytosis).

When the insulin level increases, a signal is transmitted through the IRS-PI3K-PKB pathway, which triggers the translocation of cytoplasmic vesicles to the cell periphery.

The vesicles fuse with the plasma membrane (exocytosis), delivering the transporters to the cell surface where they can mediate glucose uptake.

PKB-Protein kinase B (aka: Akt) – key role in glucose metabolism, apoptosis, cell proliferation, transcription and migration.