Insulin Signaling Pathway

Boyle - Metabolic Brain Disorders
Insulin Signal Transduction Pathway

- Primary messenger: insulin
- The release of insulin is induced by having specific levels of glucose in the blood.
- Insulin binds to the insulin receptor.
The Basics of Signaling

1. primary messenger → attaches to a receptor

2. receptors are a way to mediate information from the outside of the cell to the inside of the cell

3. once information is communicated or transduced into the cell there may be a secondary messenger (for example, cAMP or Ca++)

4. There needs to be a mechanism to terminate the signal.
ligand binds with receptor → activated

extracellular

integral protein that spans lipid bilayer membrane receptor

SIGNAL TRANSDUCTION

extracellular response

ligand is the "signal"
LIGAND GATED ION CHANNELS
G-proteins can bind GTP &/or GDP

G-proteins are heterotrimeric
attached to membrane with lipid anchors

G-protein coupled receptors

GPCR
extracellular

intracellular
G-proteins can bind GTP &/or GDP

\[ \text{receptor site} \]

\[ \text{\( \alpha \)B subunit} \]

\[ \text{GDP binds to \( \alpha \) subunit} \]

\[ \text{inactive state (GDP)} \]
G-proteins can bind GTP &/or GDP

1. When the ligand binds to receptor

   - Extracellular
   - Intracellular

   - GTP

   - Interact w/ proteins

2. Conformational change → α binds GTP

3. βγ subunit dissociate → target proteins
LONG LASTING....

WHEN BOUND \(\Rightarrow\) ACTIVE

\(\alpha\)

GTP

\(\beta\)

\(\gamma\)

extracellular

intracellular

\(\text{GPCR}\)

\(\rightarrow\) the signal stays "active" for as long as the ligand is bound to the receptor.
THE END...

LGAND IS NO LONGER BOUND

GTP is hydrolyzed to GDP

G: PROTEINS RETURN TO ORIGINAL CONFORMATIONAL STATE

extracellular

intracellular

(GPCR)
Enzyme linked receptors

- Functional domain
- Enzyme
- Ligand binding domain
- Extracellular
- Intracellular
- "Catalytic"
RTKs come in pairs

extracellular

intracellular

it has tyrosines here

most common

RECEPTOR TYROSINE KINASE

TYR TYR TYR TYR
RTK

TYR • TYR

activated

extracellular

intracellular

become a "cross linked" dimer

ONE RTK WILL P THE OTHER

ATP → ADP • P
RTK

These will serve as docking platforms for different intracellular proteins.
RTK

PROTEINS CAN Dock

extracellular

intracellular
RTK

MULTIPLE INTRACELLULAR SIGNALING PATHWAYS

IN PARALLEL

PROTEINS THAT HAVE SH2 DOMAINS CAN DOCK ON T-P

WOW!!
extracellular region

α-unit

disulfide bridge

β-unit

dimer (α-chain + β-chain)

2 α-units form a "pocket" for the insulin

extracellular

intracellular

INSULIN RECEPTOR (IR)
α-unit

Disulfide bridge extracellular

β-unit

Intracellular signaling domain

1 Spans plasma membrane

*Tyrosine protein kinase
Recall: tyrosine protein kinase

* is an enzyme, the $\text{P}^*$ tyrosine amino acids

* the protein kinase is found in the structure.
insulin $\rightarrow$ 1° messenger

$\alpha$ sub-units close-in on the insulin so that insulin cannot detach

$\beta$-subunits also move in closer to each other
That is why it is called "insulin receptor protein kinase".

As the β-subunits move closer together one subunit activates the other subunit (in the presence of ATP).
Insulin

Phosphorylated sites
insulin

activated
Insulin Receptor Substrate

Insulin

IRS-1

P sites act as attachment sites for other proteins → e.g. IRS-1
Insulin

Insulin Receptor
Substrate

IRS-1

\( \text{P} \) sites act as attachment sites for other proteins → e.g. IRS-1
IRS molecules are called adaptor proteins

IRS = insulin receptor substrate
upon binding, IRS-1 is phosphorylated by the insulin receptor kinase