Insulin Signaling Pathway

Boyle - Metabolic Brain Disorders

IRS-1
extracellular region

\[ \alpha \text{-unit} \]

\[ \beta \text{-unit} \]

dimer (\(\alpha\)-chain + \(\beta\)-chain)

disulfide bridge

2 \(\alpha\)-units form a "pocket" for the insulin

extracellular

intracellular

INSULIN RECEPTOR (IR)
**α-unit**

**β-unit**

Disulfide bridge extracellular

Intracellular signaling domain

*Tyrosine protein kinase*

Spans plasma membrane
Recall: tyrosine protein kinase is an enzyme, the tyrosine amino acids

Note: the protein kinase is found in the structure.
insulin \( \rightarrow \) 1st messenger

α subunits close in on the insulin so that insulin cannot detach

β 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.
insulin

activated.
Insulin

Insulin Receptor Substrate

IRS-1

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

Insulin Receptor Substrate

IRS-1

$\mathbf{P}$ 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
Adaptor proteins don't activate something in the pathway. It functions as an attachment point for other enzymes & proteins in the pathway.

Phosphorylated IRS-1
Insulin

Phosphorylated IRS-1

Phosphoinositide 3-kinase

Active site

Phosphorylates PIP2 → PIP3

Note: This is a lipid kinase

Regulatory region
Insulin

When PIP2 is $\text{P}$, it moves along inside membrane until it gets to

Phosphoinositide 3-kinase

PIP3-dependent protein kinase

Phosphorylated IRS-1
Insulin

PHOSPHORYLATED IRS-1

Phosphoinositide 3-kinase

PIP_3

(PDK-1)

PIP_3-dependent protein kinase

Once PDK-1 is activated then it activates PKB/Akt-1
Akt-1 = protein kinase B

- PIP3-dependent protein kinase
- Akt-1 (inactive)
- PDK-1
  - Activated Akt-1
PDK-1 activates Akt-1 (protein kinase B).

* This kinase is not membrane-bound & can diffuse all around the cell.
Akt is involved in so many critical functions.
Akt1 is a big deal - b/c it stimulates the movement of glucose membrane transporters to cell membrane
2 phosphorylates enzymes that synthesize glycogen from glucose.