Insulin Signaling Pathway-part1

Boyle - Metabolic Brain Disorders
insulin resistance

Where does it start?
Hmm, I'm hungry now...
Is your hypothalamus telling you to eat again?

Hmm, I'm hungry now...
Rich in energy
Just ate food
Hypothalamus
Info sent to hyp.
Exercising
-not so much activity

FOOD

-blood glucose levels
-insulin levels

energy balance

Exercise
**Situation A:**

1. *Just consumed a large meal* with carbs & fat
2. Rising glucose levels → insulin release
3. Insulin & glucose & leptin
4. Decrease hunger pathway in hypothalamus

**Not hungry**

**Anorexigenic pathway**

- Blood glucose levels
- Insulin levels

**Energy balance**

- Rich in energy
- Just ate food
- Not so much activity

**Hypothalamus**
**Body Mass**

- In:
  - Food Eaten
  - Hormone Levels
  - Insulin
  - Leptin

- Out:
  - Basal Metabolic Rate: ≈ 2000 cal
  - Activity: ≈ 500-1000
  - Thermogenesis
Recall - Leptin knock-out mice.

Genetics Hormonal levels etc. have a profound influence.

- Food eaten
- Hormone levels
- Insulin
- Leptin

- Basal metabolic rate ~ 2000 cal
- Activity ~ 300-1000
- Thermogenesis
ligand binds with receptor → activated

extracellular

integral protein that spans lipid bilayer membrane receptor

SIGNAL TRANSDUCTION → intracellular response

ligand is the "signal"
LIGAND GATED ION CHANNELS

- Ligand binds to channel
- Channel opens to allow ions to pass

- Closed state
- Activated state
- Open state

- Extracellular side
- Intracellular side
G-proteins can bind GTP &/or GDP

G-proteins are heterotrimeric
attached to membrane with lipid anchors

G-protein coupled receptors
G-proteins can bind GTP \&/or GDP

- receptor site

- extracellular

- intracellular

\[
\text{GDP} \quad \text{binds to } \alpha \text{ subunit}
\]

inactive state (GDP)
G-proteins can bind GTP &/or GDP

1. When the ligand binds to receptor
   - extracellular
   - intracellular

   Interact w/ proteins

   α
   GTP

   βγ

   Interact w/ other proteins

2. Conformational change → α binds GTP

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

\[\text{\textbullet} \quad \text{WHEN BOUND} \Rightarrow \text{ACTIVE}\]

\[\text{extracellular}\]

\[\text{intracellular}\]

\[\alpha \quad \text{GTP} \quad \beta \quad \gamma\]

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

UIGAND IS NO LONGER BOUND

extracellular

intracellular

G-proteins return to original conformational state

GTP is hydrolyzed to GDP

GDP
Enzyme linked receptors

- Functional domain
- Enzyme
- Ligand binding domain

- Extracellular
- Intracellular

"Catalytic"
RTKs come in pairs

It has tyrosines here

Receptor Tyrosine Kinase
RTK

> activated

TYR    TYR
TYR    TYR

extracellular

intracellular

one RTK will phosphorylate the other

ATP → ADP + P

become a "cross linked" dimer
RTK

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

Extracellular

Intracellular

Proteins can dock
RTK

MULTIPLE INTRACELLULAR SIGNALING PATHWAYS

PROTEINS THAT HAVE SH2 DOMAINS CAN DOCK ON T-P
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

spans plasma membrane

*tyrosine protein kinase
Recall: tyrosine protein kinase is an enzyme, the P tyrosine amino acids.

Note: the protein kinase is found in the structure.
Insulin $\rightarrow$ 1° messenger

α sub-units close-in on the insulin so that insulin cannot detach

β sub-units 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.

Cross-phosphorylation (in the presence of ATP).
insulin

phosphorylated sites
insulin

activated
Insulin

Insulin Receptor
Substrate

IRS-1

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

IRS-1

Insulin Receptor Substrate

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

IRS = insulin receptor substrate
Insulin

IRS-1


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 PATHWAY.
Insulin

Phosphorylated IRS-1

Phosphoinositide 3-kinase

Active site

Phosphorylates PIP2 \( \Rightarrow \) PIP3

Note this is a lipid kinase

Regulatory region
When PIP2 is phosphorylated (\(\text{P}\)), it moves along inside the membrane until it gets to phosphoinositide 3-kinase (PI3K) and PIP3-dependent protein kinase.
Insulin

PHOSPHORYLATED IRS-1

<table>
<thead>
<tr>
<th>PIP1</th>
<th>Phosphoinositide 3-kinase</th>
<th>PIP3</th>
<th>(PDK-1)</th>
<th>PIP3-dependent protein kinase</th>
</tr>
</thead>
</table>

once PDK-1 is activated then it activates PKB/Akt-1
$\text{P}$

$\text{Akt-1 = protein kinase B}$

$\text{PI}_3$-dependent protein kinase

$\text{Akt-1 (inactive)}$

$\text{Activated Akt-1}$
PDK-1 activates Akt-1 (protein kinase B).

* This kinase is not membrane-bound & can diffuse all around the cell.
Akt1 is a big deal - b/c

○ It stimulates the movement of glucose membrane transporters to cell membrane
phosphorylates enzymes that synthesize glycogen from glucose.