Hormones and Signal Transduction II

Dr. Kevin Ahern
Hormones and Signal Transduction

• G-Protein Coupled Receptors Outline
Hormones and Signal Transduction
• G-Protein Coupled Receptors Outline

Receptor
G-Proteins
Protein Kinase A
Kinase Cascade
Turning Signal Off
The Coffee Connection
Hormones and Signal Transduction
• β-adrenergic Receptor Signaling

Hormone Stimulation

ATP → cAMP

PKA → PKA-Reg

PK-P → PK

P-GP-a → GP-b

Glycogen_{x-1} → Glycogen_x

Glucose-1-phosphate
Hormones and Signal Transduction
• β-adrenergic Receptor Signaling

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Hormone Stimulation

Glycogen\(_{x-1}\)  \(\xrightarrow{\text{Glucose-1-phosphate}}\) Glycogen\(_{x}\)

\[\text{ATP} \rightarrow \text{cAMP} \rightarrow \text{PKA} \rightarrow \text{PKA-Reg} \rightarrow \text{PK} \rightarrow \text{PK-P} \rightarrow \text{P-GP-a} \rightarrow \text{GP-b} \rightarrow \text{GS} \rightarrow \text{GS-P} \rightarrow \text{Adenylate Cyclase} \rightarrow \text{ATP} \]
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

1. Hormone Stimulation

2. ATP → cAMP

- PKA
- PKA-Reg
- PK-P
- PK
- P-GP-a
- GP-b

GS-P → GS

Glycogen\(_{x-1}\) → Glycogen\(_x\)

Glucose-1-phosphate
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

1. Hormone Stimulation

2. ATP

3. cAMP

Glycogen_{x-1} \xleftarrow{\text{Glucose-1-phosphate}} \text{Glycogen}_x
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

1. Hormone Stimulation

2. Adrenergic Receptor

3. cAMP

4. PKA-Reg

Protein Kinase A

GS-P

GS

PK-P

PK

P-GP-a

GP-b

Glycogen_{x-1}

Glycogen_x

Glucose-1-phosphate

ATP
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

1. Hormone Stimulation

2. ● Adenylate Cyclase
   - ATP → cAMP

3. cAMP → PKA

4. PKA → PKA-Reg

5. PKA → PK-P → PK

GS-P → GS

P-GP-a → GP-b

Glucose-1-phosphate → Glycogen

Glycogen → Glycogen

Protein Kinase A

Phosphorylase Kinase
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

1. Hormone Stimulation

2. ATP → cAMP

3. cAMP → PKA-Reg

4. PKA-Reg → PK-P

5. PK-P → PK

5a. PK → Protein Kinase A

GS-P → GS

Glycogen Synthase

Glycogen

Glycogen

Glycogen

Glucose-1-phosphate
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

1. Hormone Stimulation
2. ATP → cAMP
3. cAMP activates Protein Kinase A (PKA)
4. PKA phosphorylates Phosphorylase Kinase (PK-P)
5. PK-P phosphorylates Glycogen Phosphorylase (GP-b)
6. GP-b dephosphorylates Glycogen

GS = Glycogen Synthase

Glucose-1-phosphate

Glycogen

Glycogen

Glycogen

Glycogen

Glycogen
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

1. Hormone Stimulation

2. ATP → cAMP

3. cAMP → PKA

4. PKA → PKA-Reg

5. PKA → PK-P

6. PK-P → PK

7. PK → Glycogen Phosphorylase

Glycogen Synthase → GS-P → GS

Glycogen → Glucose-1-phosphate

Protein Kinase A

Phosphorylase Kinase

Glycogen Phosphorylase
Hormones and Signal Transduction

- PKA Activation

Protein Kinase A (PKA) has 2 catalytic subunits and 2 regulatory subunits.

\[ + \text{cAMP} \rightarrow \text{cAMP binding to PKA releases catalytic subunits from regulatory subunits, and allows catalytic subunits to phosphorylate their substrates} \]
Hormones and Signal Transduction
• Turning Off β-adrenergic Receptor Signaling
Hormones and Signal Transduction
  • Turning Off β-adrenergic Receptor Signaling

Turning off the Signaling Pathway

![Signal Transduction Diagram]
Hormones and Signal Transduction

• Turning Off β-adrenergic Receptor Signaling

Turning off the Signaling Pathway

β-adrenergic Receptor
Hormones and Signal Transduction

• Turning Off β-adrenergic Receptor Signaling

Turning off the Signaling Pathway

β-adrenergic Receptor
G-Protein
Hormones and Signal Transduction

• Turning Off β-adrenergic Receptor Signaling

Turning off the Signaling Pathway

β-adrenergic Receptor
G-Protein
cAMP

Diagram: Hormone stimulation activates the β-adrenergic receptor, which in turn activates a G-protein, leading to the production of cAMP. cAMP activates PKA, which then phosphorylates glycogen to form glucose-1-phosphate. The reverse reaction converts glucose-1-phosphate back to glycogen.
Hormones and Signal Transduction

• Turning Off $\beta$-adrenergic Receptor Signaling

Turning off the Signaling Pathway

$\beta$-adrenergic Receptor
G-Protein
cAMP
Protein Kinase A

Glucose-1-phosphate

Glycogen$_{x-1}$ $\rightarrow$ Glycogen$_x$
Hormones and Signal Transduction

• Turning Off β-adrenergic Receptor Signaling

Turning Off β-adrenergic Receptor
Hormones and Signal Transduction
• Turning Off β-adrenergic Receptor Signaling

Turning Off β-adrenergic Receptor

Exterior of Cell

Cytoplasm
Hormones and Signal Transduction
• Turning Off β-adrenergic Receptor Signaling

Exterior of Cell

Turning Off β-adrenergic Receptor

Cytoplasm

ATP → ADP

G-Protein Receptor Kinase

PO₄
Hormones and Signal Transduction

• Turning Off β-adrenergic Receptor Signaling

Turning Off β-adrenergic Receptor

Exterior of Cell

Cytoplasm

G-Protein Receptor Kinase

ATP, ADP

Arrestin
Hormones and Signal Transduction

• Turning Off β-adrenergic Receptor Signaling

Exterior of Cell

Turning Off β-adrenergic Receptor

Cytoplasm

ATP → ADP

G-Protein Receptor Kinase

Arrestin
• Turning Off β-adrenergic Receptor Signaling

Exterior of Cell

Cytoplasm

Turning Off β-adrenergic Receptor

ATP → ADP

G-Protein Receptor Kinase

Arrestin

Blocks and Favors Endocytosis
Hormones and Signal Transduction
  • β-adrenergic Receptor Signaling

G-protein Inactivation
Hormones and Signal Transduction
  • β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Inherent GTPase Activity
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Inherent GTPase Activity
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Inherent GTPase Activity

Hydrolysis

Phosphate
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Inherent GTPase Activity

Hydrolysis
Phosphate
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Inherent GTPase Activity

Hydrolysis
Phosphate
Hormones and Signal Transduction
• β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Inherent GTPase Activity

[Diagram showing G-protein inactivation with hydrolysis of GTP to GDP and release of phosphate.]
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

G-protein Inactivation

Auto-regulating
Inherent GTPase Activity

Hydrolysis

Phosphate

Return to Resting State
**Hormones and Signal Transduction**

- β-adrenergic Receptor Signaling

**G-protein Inactivation**

Auto-regulating

Inherent GTPase Activity

- Hydrolysis
- Return to Resting State
- Adenylate Cyclase Inactivated - no more cAMP
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

PO₄⁻ → Adenylyl Cyclase → cAMP → ATP → PKA → PKA-Reg → GS-P → GS

Glycogen_{x-1} → Glycogen_{x} → Glucose-1-phosphate
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

PO₄⁻

Adenylyl Cyclase

ATP

cAMP

PKA

PK-P

PKA-Reg

GS-P

GS

P-GP-a

GP-b

Glycogenₓ⁻¹

Glycogenₓ

Glucose-1-phosphate
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling
Hormones and Signal Transduction
• β-adrenergic Receptor Signaling

\[
PO_4^-= PO_4^-= X
\]
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

Diagram:
- cAMP
- PKA
- GS-P
- PK-P
- P-GP-a
- Glycogen
- Glucose-1-phosphate
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

- cAMP
- PKA
- GS-P
- PK-P
- P-GP-a
- Glycogen
- Glucose-1-phosphate
- Phosphodiesterase
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

PKA

GS-P

PK-P

P-GP-α

Glycogen x

Glycogen x-1

Glucose-1-phosphate

PO₄ =

Phosphodiesterase

AMP
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling

![Diagram showing the interaction between Adenylate Cyclase (AC) and PKA, with the conversion of cAMP to AMP by Phosphodiesterase and its inactivation.]

PKA → Phosphodiesterase

AMP

Becomes Inactive
Hormones and Signal Transduction

• β-adrenergic Receptor Signaling
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

\[ \text{GS-P} \rightarrow \text{PKA} \rightarrow \text{P-GP-a} \]

Glycogen → Glucose-1-phosphate

\[ \text{PO}_4 = \text{Phosphodiesterase} \]

Phosphodiesterase is Inhibited by Caffeine

\[ \text{cAMP} \rightarrow \text{AMP} \]
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling

Drinking Coffee Gives a Small Boost to Blood Glucose by Keeping cAMP Levels Higher
Hormones and Signal Transduction

- β-adrenergic Receptor Signaling
Receptor Tyrosine Kinases (RTKs)
Receptor Tyrosine Kinases (RTKs)

RTKs are Membrane Bound Proteins that Phosphorylate Tyrosines
Receptor Tyrosine Kinases (RTKs)

RTKs are Membrane Bound Proteins that Phosphorylate Tyrosines
RTKs Play Important Roles in Regulating Cell Proliferation
Receptor Tyrosine Kinases (RTKs)

RTKs are Membrane Bound Proteins that Phosphorylate Tyrosines
RTKs Play Important Roles in Regulating Cell Proliferation
Dimerization Important for Activity
**Receptor Tyrosine Kinases (RTKs)**

RTKs are Membrane Bound Proteins that Phosphorylate Tyrosines
RTKs Play Important Roles in Regulating Cell Proliferation
Dimerization Important for Activity
Receptor Tyrosine Kinases (RTKs)
Lipid Bilayer

Receptor Tyrosine Kinases (RTKs)
Receptor Tyrosine Kinases (RTKs)

Lipid Bilayer

Outside of Cell

Inside of Cell (Cytoplasm)
Receptor Tyrosine Kinases (RTKs)

Lipid Bilayer

RTK Monomer → Outside of Cell

Inside of Cell (Cytoplasm)

RTK Monomer ← RTK Monomer
Receptor Tyrosine Kinases (RTKs)

- **RTK Monomer**
  - Outside of Cell
  - Inside of Cell (Cytoplasm)
- **Lipid Bilayer**
- **Transmembrane α-helix**

RTK Monomer

- RTK Monomer
Receptor Tyrosine Kinases (RTKs)

Lipid Bilayer

Transmembrane α-helix

Outside of Cell

RTK Monomer

Inside of Cell (Cytoplasm)

Cytoplasmic Tyrosine Kinase Domain (inactive)

RTK Monomer

Receptor Tyrosine Kinases (RTKs)
Receptor Tyrosine Kinases (RTKs)
Ligand (Hormone)

Binding & Dimerization

Receptor Tyrosine Kinases (RTKs)
Ligand (Hormone) Binding & Dimerization

Receptor Tyrosine Kinases (RTKs)
Receptor Tyrosine Kinases (RTKs)

Ligand (Hormone) Binding & Dimerization

Activation of Tails Autophosphorylation
Receptor Tyrosine Kinases (RTKs)

Ligand (Hormone) Binding & Dimerization

Activation of Tails Autophosphorylation
Ligand (Hormone) Binding & Dimerization

Activation of Tails Autophosphorylation

Active Tyrosine Kinase

Receptor Tyrosine Kinases (RTKs)
Receptor Tyrosine Kinases (RTKs)
Receptor Tyrosine Kinases (RTKs)

Assembly of Signaling Complex
Assembly of Signaling Complex

Receptor Tyrosine Kinases (RTKs)
Receptor Tyrosine Kinases (RTKs)

Assembly of Signaling Complex
Assembly of Signaling Complex

Receptor Tyrosine Kinases (RTKs)

SH2 Domains of Proteins Recognize and Bind Phosphotyrosines
Receptor Tyrosine Kinases (RTKs)

Assembly of Signaling Complex

SH2 Domains of Proteins Recognize and Bind Phosphotyrosines

Signaling Complex Communicates Message to Cell (usually by phosphorylation)
Receptor Tyrosine Kinases (RTKs)

- RTK Signaling Overview
Receptor Tyrosine Kinases (RTKs)

- RTK Signaling Overview

Binding of Hormone to RTK in Membrane
Receptor Tyrosine Kinases (RTKs)

- RTK Signaling Overview

Binding of Hormone to RTK in Membrane

Receptor Dimerization
Receptor Tyrosine Kinases (RTKs)

- RTK Signaling Overview

- Binding of Hormone to RTK in Membrane
- Receptor Dimerization
- Autophosphorylation
Receptor Tyrosine Kinases (RTKs)

- RTK Signaling Overview

1. Binding of Hormone to RTK in Membrane
2. Receptor Dimerization
3. Autophosphorylation
4. Signaling Complex Assembly
Receptor Tyrosine Kinases (RTKs)

- RTK Signaling Overview

1. Binding of Hormone to RTK in Membrane
2. Receptor Dimerization
3. Autophosphorylation
4. Signaling Complex Assembly
5. Communicate Message to Cell
RTKs - Insulin Receptor
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
**RTKs - Insulin Receptor**

Unlike Other RTKs, Always a Dimer in Membrane

Binding of Insulin Activates Autophosphorylation of Tails
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails
**RTKs - Insulin Receptor**

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails

Binding of Insulin $\rightarrow$ Autophosphorylation
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane

Binding of Insulin Activates Autophosphorylation of Tails

Binding of Insulin ➔ Autophosphorylation ➔ IRS-1 Activation
**RTKs - Insulin Receptor**

Unlike Other RTKs, Always a Dimer in Membrane

Binding of Insulin Activates Autophosphorylation of Tails

Other Signaling Pathways

- Binding of Insulin
- Autophosphorylation
- IRS-1 Activation
- PI3 Kinase Activation
Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails

Other Signaling Pathways

Binding of Insulin $\rightarrow$ Autophosphorylation $\rightarrow$ IRS-1 Activation $\rightarrow$ PI$_3$ Kinase Activation $\rightarrow$ PIP3 Formation $\rightarrow$ PDK1 Activation
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails

Other Signaling Pathways

Binding of Insulin → Autophosphorylation → IRS-1 Activation → PI3 Kinase Activation → PIP3 Formation → PDK1 Activation → Akt Kinase Activation
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails

Binding of Insulin → Autophosphorylation → IRS-1 Activation → PI3 Kinase Activation → PIP3 Formation → PDK1 Activation → Akt Kinase Activation → Stimulate GLUT4 Movement to Cytoplasm

Other Signaling Pathways
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails

Other Signaling Pathways

Binding of Insulin → Autophosphorylation → IRS-1 Activation → PI3 Kinase Activation → PIP3 Formation → PDK1 Activation → Akt Kinase Activation → Stimulate GLUT4 Movement to Cytoplasm → Cells Uptake Glucose

- PI
- PIP3
- PDK1
- Akt Kinase
- GLUT4
- Cells Uptake Glucose
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails

Other Signaling Pathways

Binding of Insulin → Autophosphorylation → IRS-1 Activation → PI3 Kinase Activation → PIP3 Formation → PDK1 Activation → Akt Kinase Activation

Stimulate GLUT4 Movement to Cytoplasm

Blood Glucose Levels Fall

Cells Uptake Glucose

Stimulate GLUT4 Movement to Cytoplasm
RTKs - Insulin Receptor

Unlike Other RTKs, Always a Dimer in Membrane
Binding of Insulin Activates Autophosphorylation of Tails

Insulin Signaling Also Activates Phosphoprotein Phosphatase

Blood Glucose Levels Fall

Cells Uptake Glucose

Stimulate GLUT4 Movement to Cytoplasm
Hormones and Signal Transduction

β- Adrenergic Pathway

Insulin Receptor Pathway
Hormones and Signal Transduction

β- Adrenergic Pathway

\[ \text{G-Protein} \rightarrow \text{Adenylate Cylase} \rightarrow \text{cAMP} \rightarrow \text{PKA Active} \rightarrow \text{PK Active} \rightarrow \text{GS Inactive} \rightarrow \text{GP-a Active} \]
Hormones and Signal Transduction

β- Adrenergic Pathway

G-Protein

Adenylate Cylase

cAMP

PKA Active

PK Active

GS Inactive

GP-a Active

Glycogen Broken Down

Blood Glucose Levels Rise
Hormones and Signal Transduction

β- Adrenergic Pathway

G-Protein
↓
Adenylate Cylase
↓
cAMP
↓
PKA Active
↓
PK
Active
↓
GS
Inactive
↓
GP-a
Active
↓
Glycogen Broken Down
↓
Blood Glucose Levels Rise

PK, GP-a Inactive
↑
GS Active
↓
Phosphoprotein Phosphatase Activated

Glucose Taken Into Cell
↓
GLUT4 Moved to Cytoplasm
↓
Akt Kinase Activation
↓
PDK1 Activation
↓
PIP3 Formation
↓
Pl3 Kinase Activation
↓
IRS-1 Activation
↓
Tyrosine Kinase Activation
↓
Insulin Receptor Pathway
Hormones and Signal Transduction

β- Adrenergic Pathway

- G-Protein
- Adenylate Cylase
  - cAMP
  - PKA Active
    - PK Active
    - GS Inactive
    - GP-a Active
- Glycogen Broken Down
- Blood Glucose Levels Rise

Blood Glucose Levels Fall

- Glucose Taken Into Cell
- GLUT4 Moved to Cytoplasm
- Akt Kinase Activation
- PDK1 Activation
- PIP3 Formation
- PI3 Kinase Activation
- IRS-1 Activation
- Tyrosine Kinase Activation

Phosphoprotein Phosphatase Activated

PK, GP-a Inactive
GS Active

Glycogen Made

Insulin Receptor Pathway
RTKs - Epidermal Growth Factor
RTKs - Epidermal Growth Factor

Receptor Tyrosine Kinase
RTKs - Epidermal Growth Factor

Receptor Tyrosine Kinase
Dimerizes on Binding Epidermal Growth Factor (EGF)
RTKs - Epidermal Growth Factor

Receptor Tyrosine Kinase
Dimerizes on Binding Epidermal Growth Factor (EGF)
Involved in Growth, Proliferation and Cell Differentiation
RTKs - Epidermal Growth Factor

Receptor Tyrosine Kinase
Dimerizes on Binding Epidermal Growth Factor (EGF)
Involved in Growth, Proliferation and Cell Differentiation

EGFR
RTKs - Epidermal Growth Factor

Receptor Tyrosine Kinase
Dimerizes on Binding Epidermal Growth Factor (EGF)
Involved in Growth, Proliferation and Cell Differentiation
Epidermal Growth Factor Receptor (EGFR)
RTKs - Epidermal Growth Factor

Epidermal Growth Factor Receptor (EGFR)

EGFR Signaling, Part 1
Epidermal Growth Factor Receptor (EGFR)

EGFR Signaling, Part 1

RTKs - Epidermal Growth Factor

EGFR Dimer
Epidermal Growth Factor Receptor (EGFR)

EGFR Signaling, Part 1
RTKs - Epidermal Growth Factor

Epidermal Growth Factor Receptor (EGFR)

EGFR Signaling, Part 1

- EGFR Dimer
- Autophosphorylated Tyrosines in Cytoplasmic Domain
- Signaling Complex Assembled on Phosphotyrosines
Epidermal Growth Factor Receptor (EGFR)

EGFR Signaling, Part 1
Epidermal Growth Factor Receptor (EGFR) Signaling, Part 1

- Epidermal Growth Factor (EGF)
- EGFR Dimer
- Autophosphorylated Tyrosines in Cytoplasmic Domain
- Signaling Complex Assembled on Phosphotyrosines
Epidermal Growth Factor Receptor (EGFR)

EGFR Signaling, Part 1

- EGFR Dimer
- Autophosphorylated Tyrosines in Cytoplasmic Domain
- Signaling Complex Assembled on Phosphotyrosines

Prepares Cell for Division
Metabolic Melody
In My Liver
(to the tune of “And I Love Her”)
Copyright © Kevin Ahern
In My Liver
(to the tune of “And I Love Her”)

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If I am missing meals
On busy days
That’s when my body steals
Glucose away
From my liver

It starts with glucagon
When I’m weak kneed
The hormone acts to spawn
New energy
In my liver

Bridge

The signaling
Acts rapidly
c-A-M-P’s
Fire up kinase
In My Liver
(to the tune of “And I Love Her”)

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If I am missing meals
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The hormone acts to spawn
New energy
In my liver

Bridge
The signaling
Acts rapidly
c-A-M-P’s
Fire up kinase

Phosphorylase then gets
Re-activated
So glycogen begets
Glucose phosphated
In my liver

Instrumental

Then in the last step here
A phosphatase
Makes phosphate disappear
With no delays
In my liver