Hormones and Signal Transduction

Dr. Kevin Ahern
Signaling

- Outline
Signaling

• Outline

Background
Signaling

- Outline

Background
Membranes
Signaling
• Outline

Background
Membranes
Hormones & Receptors
Signaling
• Outline

Background
Membranes
Hormones & Receptors
Second Messengers
Signaling
• Introduction
Needs of a Multicellular Organism
Needs of a Multicellular Organism
Responding to Environment
Needs of a Multicellular Organism

Responding to Environment

Food Status
Needs of a Multicellular Organism

Responding to Environment
Food Status
Danger
Signaling

- Introduction

Needs of a Multicellular Organism

- Responding to Environment
- Food Status
- Danger
- Growth
Needs of a Multicellular Organism

- Responding to Environment
- Food Status
- Danger
- Growth
- Injury
Coordination of Cellular/Tissue Responses
Coordination of Cellular/Tissue Responses
Signaling

Signal binds receptor → One or more intermediary molecules → Changes in target molecules cause changes in metabolic pathways, gene expression, etc.
Signaling
- Membranes
Lipid Bilayer Prevents Entry of Most Molecules
Lipid Bilayer Prevents Entry of Most Molecules
Signaling
• Membranes

Lipid Bilayer Prevents Entry of Most Molecules

Lipid Bilayer

Organization of Bilayer Around Cell
Lipid Bilayer Prevents Entry of Most Molecules

Information must move across membrane
Signaling
Membranes

Lipid Bilayer Prevents Entry of Most Molecules

Lipid Bilayer

Organization of Bilayer Around Cell

Information must move across membrane
Signal Transduction
Signaling

Ligand-gated ion channel

Ligand

Ca^{2+}
Simplest Signaling
Simplest Signaling

Signal

Ligand

Ca$^{2+}$

Ligand-gated ion channel
Simplest Signaling

Signal

Response

Ligand

Ca^{2+}

Ligand-gated ion channel
Nerve System Signaling
Hormones and Signal Transduction

- Hormones
Hormones and Signal Transduction

- Hormones

Hormones Communicate Messages
Hormones and Signal Transduction

• Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Hormones and Signal Transduction

- Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Exert Effects in Other Part of Body
Hormones and Signal Transduction

• Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Exert Effects in Other Part of Body
First Messengers of a Multi-component Message
Hormones and Signal Transduction

- Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Exert Effects in Other Part of Body
First Messengers of a Multi-component Message
Numerous Chemical Forms
Hormones and Signal Transduction

- Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Exert Effects in Other Part of Body
First Messengers of a Multi-component Message
Numerous Chemical Forms

Thyroid Hormone
Hormones and Signal Transduction

- Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Exert Effects in Other Part of Body
First Messengers of a Multi-component Message
Numerous Chemical Forms

Epinephrine

Thyroid Hormone
Hormones and Signal Transduction

• Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Exert Effects in Other Part of Body
First Messengers of a Multi-component Message
Numerous Chemical Forms

Epinephrine

Thyroid Hormone

Epidermal Growth Factor
Hormones and Signal Transduction

• Hormones

Hormones Communicate Messages
Hormones are Made in One Part of the Body
Exert Effects in Other Part of Body
First Messengers of a Multi-component Message
Numerous Chemical Forms

Epinephrine

Thyroid Hormone

Epidermal Growth Factor

Progesterone
Hormones and Signal Transduction

• Introduction
Hormones and Signal Transduction

• Introduction

Cellular Signaling Has Complexity
Hormones and Signal Transduction

- Introduction

Cellular Signaling Has Complexity
Responses Aimed at Benefitting Organism
Hormones and Signal Transduction

- Binding to Receptor
Hormones and Signal Transduction

• Binding to Receptor
Hormones and Signal Transduction

- Binding to Receptor

Steroid Hormones Diffuse Through Membrane
Hormones and Signal Transduction
• Binding to Receptor

Steroid Hormones Diffuse Through Membrane

Cytosolic Receptor
Hormones and Signal Transduction

- Binding to Receptor

Steroid Hormones Diffuse Through Membrane
Cytosolic Receptor

Receptor Binding Inside Cell
Hormones and Signal Transduction

- Binding to Receptor

Steroid Hormones Diffuse Through Membrane
Cytosolic Receptor

Receptor Binding Inside Cell
**Hormones and Signal Transduction**

- Binding to Receptor

- Steroid Hormones Diffuse Through Membrane

- Cytosolic Receptor

- Non-steroid Hormone

- Receptor Binding Inside Cell
Hormones and Signal Transduction

- Binding to Receptor

Steroid Hormones Diffuse Through Membrane

Cytosolic Receptor

Receptor Binding Outside of Cell

Non-steroid Hormone

Receptor Binding Inside Cell
Hormones and Signal Transduction
• Binding to Receptor

Steroid Hormones Diffuse Through Membrane
Cytosolic Receptor

Receptor Binding Outside of Cell
Non-steroid Hormone
Numerous Internal Message Carriers

Receptor Binding Inside Cell
Hormones and Signal Transduction

• Receptors
Hormones and Signal Transduction

- Receptors

Interaction of Hormone with Receptor Changes Receptor
Hormones and Signal Transduction

- Receptors

Interaction of Hormone with Receptor Changes Receptor
Receptor Change Alters Interactions with Other Proteins
Hormones and Signal Transduction

- Receptors

Interaction of Hormone with Receptor Changes Receptor
Receptor Change Alters Interactions with Other Proteins

Changes on Hormone Binding
Hormones and Signal Transduction
• Membrane-bound Receptors

G-Protein Coupled Receptor
Hormones and Signal Transduction
G-protein Coupled Receptors (GPCRs)
Hormones and Signal Transduction

G-protein Coupled Receptors (GPCRs)

Almost 800 Genes in Human Genome
Hormones and Signal Transduction
G-protein Coupled Receptors (GPCRs)

Almost 800 Genes in Human Genome
460 Olfactory
Hormones and Signal Transduction
G-protein Coupled Receptors (GPCRs)

Almost 800 Genes in Human Genome
460 Olfactory
β-adrenergic Receptor
Hormones and Signal Transduction
G-protein Coupled Receptors (GPCRs)

Almost 800 Genes in Human Genome
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β-adrenergic Receptor
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Almost 800 Genes in Human Genome
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Hormones and Signal Transduction
G-protein Coupled Receptors (GPCRs)

Almost 800 Genes in Human Genome
460 Olfactory
β-adrenergic Receptor

Membrane Bound

Extracellular Domain

Seven Transmembrane Domains
Hormones and Signal Transduction
G-protein Coupled Receptors (GPCRs)

Almost 800 Genes in Human Genome
460 Olfactory
β-adrenergic Receptor
GPCR Action Cycle
GPCR Action Cycle

1. GPCR activation
2. G protein coupling
3. G protein activation
4. GTP hydrolysis
5. G protein inactivation
6. Return to resting state

GTPase action
Hormone
Binding of Hormone

Hormone

Structural Change of Receptor

GTPase action

1

2

3

4

5

6
Binding of Hormone

Structural Change of Receptor

Hormone

Replacement of GDP by GTP

GTPase action

1. Hormone binding
2. Structural change
3. Replacement of GDP by GTP
4. GTPase action
5. Structural change
6. Hormone binding
Binding of Hormone

Hormone

Structural Change of Receptor

Replacement of GDP by GTP

Activation of an Enzyme

GTPase action
Binding of Hormone

Hormone

Structural Change of Receptor

Replacement of GDP by GTP

Activation of an Enzyme

Return to Original State
Hormones and Signal Transduction

- Receipt of Message
Hormones and Signal Transduction

• Receipt of Message

Membrane Receptor Proteins Internalize Message
Hormones and Signal Transduction

- Receipt of Message

Membrane Receptor Proteins Internalize Message
Induce Activation of Synthesis of Second Messengers
Hormones and Signal Transduction
• Receipt of Message

Membrane Receptor Proteins Internalize Message
Activate Synthesis of Second Messengers

Inositol 1,4,5 Trisphosphate (IP$_3$)
Hormones and Signal Transduction

• Receipt of Message

Membrane Receptor Proteins Internalize Message
Activate Synthesis of Second Messengers

Inositol 1,4,5 Trisphosphate (IP$_3$)

Cyclic AMP (cAMP)
Hormones and Signal Transduction

- Receipt of Message

Membrane Receptor Proteins Internalize Message
Activate Synthesis of Second Messengers

- Inositol 1,4,5 Trisphosphate (IP₃)
- Cyclic AMP (cAMP)
- Calcium Ions
Hormones and Signal Transduction

• Receipt of Message

Membrane Receptor Proteins Internalize Message
Activate Synthesis of Second Messengers

- Inositol 1,4,5 Trisphosphate (IP$_3$)
- Cyclic AMP (cAMP)
- Calcium Ions
- Cyclic GMP (cGMP)
Hormones and Signal Transduction

- Receipt of Message

Membrane Receptor Proteins Internalize Message
Activate Synthesis of Second Messengers
Covalent Modification of “Downstream” Proteins

Inositol 1,4,5 Trisphosphate (IP$_3$)

Cyclic AMP (cAMP)

Cyclic GMP (cGMP)

Calcium Ions
Hormones and Signal Transduction

- Receipt of Message

Membrane Receptor Proteins Internalize Message
- Activate Synthesis of Second Messengers
- Covalent Modification of “Downstream” Proteins
- Alteration of Gene Expression

- Inositol 1,4,5 Trisphosphate (IP$_3$)
- Cyclic AMP (cAMP)
- Calcium Ions
- Cyclic GMP (cGMP)
Hormones and Signal Transduction

- Receipt of Message

Membrane Receptor Proteins Internalize Message
Activate Synthesis of Second Messengers
Covalent Modification of “Downstream” Proteins
Alteration of Gene Expression
Change of Enzyme Activities

Inositol 1,4,5 Trisphosphate (IP$_3$)

Cyclic AMP (cAMP)

Calcium Ions

Cyclic GMP (cGMP)
Hormones and Signal Transduction
  • GPCRs and G-Proteins
Hormones and Signal Transduction

- GPCRs and G-Proteins
Hormones and Signal Transduction
• GPCRs and G-Proteins

Resting State
Hormones and Signal Transduction

• GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Hormones and Signal Transduction

• GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Heterotrimeric - α,β,γ Subunits

Resting State
Hormones and Signal Transduction
- GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Heterotrimeric - α,β,γ Subunits
Associate with GPCRs

Resting State
Hormones and Signal Transduction
  • GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Heterotrimeric - α,β,γ Subunits
Associate with GPCRs
Altered by GPCR’s Binding of Hormone

Resting State
Hormones and Signal Transduction

• GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Heterotrimeric - α,β,γ Subunits
Associate with GPCRs
Altered by GPCR’s Binding of Hormone

Epinephrine
Hormones and Signal Transduction

- GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Heterotrimeric - α, β, γ Subunits
Associate with GPCRs
Altered by GPCR’s Binding of Hormone

Resting State
**Hormones and Signal Transduction**

- GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Heterotrimeric - α,β,γ Subunits
Associate with GPCRs
Altered by GPCR’s Binding of Hormone

![Diagram of GPCR and G-Protein interaction](image)
Hormones and Signal Transduction

• GPCRs and G-Proteins

G-Proteins Bind Guanine Nucleotides (GDP and GTP)
Heterotrimeric - α,β,γ Subunits
Associate with GPCRs
Altered by GPCR’s Binding of Hormone
Hormones and Signal Transduction

β-adrenergic Receptor Signaling

Creation of the Second Messenger
Hormones and Signal Transduction

β-adrenergic Receptor Signaling

Creation of the Second Messenger
Hormones and Signal Transduction
β-adrenergic Receptor Signaling

Creation of the Second Messenger

Adenylate Cyclase
Hormones and Signal Transduction

β-adrenergic Receptor Signaling

Creation of the Second Messenger

Adenylate Cyclase

Also Membrane Bound
Hormones and Signal Transduction

β-adrenergic Receptor Signaling

Creation of the Second Messenger

Also Membrane Bound
**Hormones and Signal Transduction**

β-adrenergic Receptor Signaling

Creation of the Second Messenger

Adenylate Cyclase

Also Membrane Bound

Activated by binding to α-subunit of G-protein
**Hormones and Signal Transduction**

β-adrenergic Receptor Signaling

Creation of the Second Messenger

Adenylate Cyclase

Activated by binding to α-subunit of G-protein

Also Membrane Bound

AfT

+ PPi

Adenylate Cyclase
Hormones and Signal Transduction
β-adrenergic Receptor Signaling

Creation of the Second Messenger

Adenylate Cyclase
Also Membrane Bound

Activated by binding to α-subunit of G-protein

ATP

cAMP + PPi

Second Messenger
Hormones and Signal Transduction
β-adrenergic Receptor Signaling

At the level of the cell, the activated α-subunit of G-protein

Firstly, Adenylate Cyclase is activated by binding to α-subunit of G-protein:

Activated by binding to α-subunit of G-protein

Transmits Signal

Adenylate Cyclase

Second Messenger

ATP

+ PPi

cAMP

Also Membrane Bound

Creation of the Second Messenger
Hormones and Signal Transduction

- Actions of the Second Messenger

4 cAMP
Hormones and Signal Transduction
• Actions of the Second Messenger

Protein Kinase A

4 cAMP

\[ \text{R} \quad \text{C} \]
\[ \text{R} \quad \text{C} \]
Hormones and Signal Transduction
- Actions of the Second Messenger

Protein Kinase A

4 cAMP

(Inactive)
Hormones and Signal Transduction

• Actions of the Second Messenger

Protein Kinase A

(Inactive)
Hormones and Signal Transduction
• Actions of the Second Messenger

Protein Kinase A
(Inactive)

4 cAMP

Catalytic Subunits
Hormones and Signal Transduction

• Actions of the Second Messenger

Protein Kinase A

4 cAMP

Regulatory Subunits

+Catalytic Subunits

(Inactive)
Hormones and Signal Transduction

- Actions of the Second Messenger

Protein Kinase A

4 cAMP

(Inactive)

Activated
Hormones and Signal Transduction

• Actions of the Second Messenger

Protein Kinase A

\[
\begin{align*}
\text{Inactive} & \quad \text{4 cAMP} \\
\text{(Inactive)} & \quad \text{Activated}
\end{align*}
\]

\[
\begin{align*}
\text{Ser/Thr} & \quad \text{Phosphoprotein} \\
\text{ATP} & \quad \text{ADP}
\end{align*}
\]
Hormones and Signal Transduction

• Actions of the Second Messenger

Protein Kinase A

4 cAMP

(R) (C) (R) (C)

(Inactive)

Activated

Activity Altered by Phosphorylation

Ser/Thr

ATP

ADP

Phosphoprotein
Metabolic Melody
The Tao of Hormones
(To the tune of "The Sound of Silence")
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Metabolic Melody
The Tao of Hormones
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Biochemistry my friend
It's time to study you again
Mechanisms that I need to know
Are the things that really stress me so
"Get these pathways planted firmly in your head,"
Ahern said
Let's start with ep-inephrine
Membrane proteins are well known
Changed on binding this hormone
Rearranging selves without protest
Stimulating a G alpha S
To go open up and displace its GDP
With GTP
Because of ep-inephrine
Active G then moves a ways
Stimulating ad cyclase
So a bunch of cyclic AMP
Binds to kinase and then sets it free
All the active sites of the kinases await
Triphosphate
Because of ep-inephrine
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Stimulating ad cyclase
So a bunch of cyclic AMP
Binds to kinase and then sets it free
All the active sites of the kinases await
Triphosphate
Because of ep-inephrine

Muscles are affected then
Breaking down their glycogen
So they get a wad of energy
In the form of lots of G-1-P
And the synthases that could make a glucose chain
All refrain
Because of ep-inephrine
Now I've reached the pathway end
Going from adrenalin
Here's a trick I learned to get it right
Linking memory to flight or fright
So the mechanism that's the source of anxious fears
Reappears
When I make ep-inephrine