# Chem 452 - Lecture 10
# Signal Transduction
# 111130

Here we look at the movement of a signal from the outside of a cell to its inside, where it elicits changes within the cell. These changes are usually mediated by protein kinases, which phosphorylate enzymes to turn them on or off. We will focus on three examples; the β-adrenergic receptor, which is involved in the "flight or fight response, the insulin receptor, which is involved in regulating blood glucose levels, and the epidermal growth factor (EGF) receptor, which triggers cell growth in response to injury. Each example presents common themes such as secondary messengers, the amplification of a signal, and the activation of protein kinases. These signal pathways also provide examples of how multiple proteins can work together in complex ways to produce a concerted result.

## Introduction

- Signal transduction involves the changing of a cell's metabolism or gene expression in response to an external stimulus.
- We will focus on three examples
  - The hormone **epinephrine** (adrenalin)
    - Regulates the "flight or fight response"
  - The hormone **insulin**
    - Regulates blood glucose levels after a meal
  - The hormone **epidermal growth factor** (EGF)
    - Stimulates cell growth after injury



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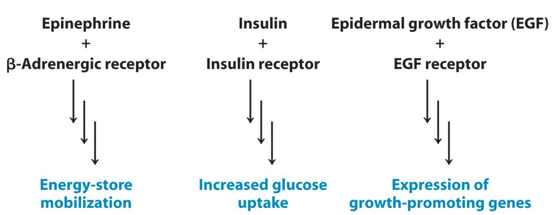




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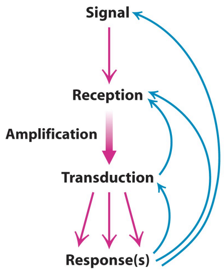




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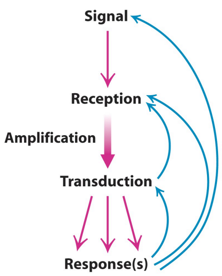


- Release of primary messenger
  - epinephrine
  - insulin
  - EGF
- Reception of primary message
- Delivery of message inside the cell
  - cAMP
  - $Ca^{2+}$
  - inositol 1,4,5-triphosphate ($IP_3$)
  - diacylglycerol (DAG)
- Activation of effectors
- Termination of the Signal



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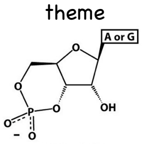
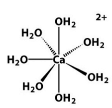
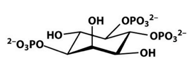


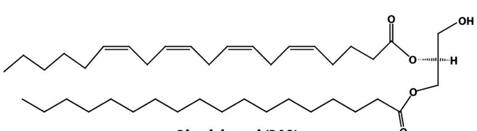

**cAMP, cGMP**



**Calcium ion**



**Inositol 1,4,5-trisphosphate ($IP_3$)**



**Diacylglycerol (DAG)**



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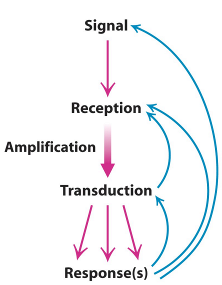


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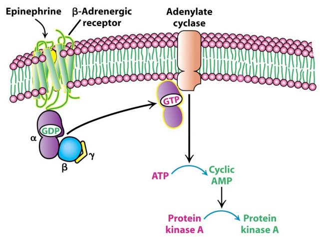
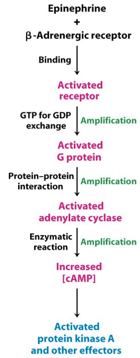
# G-Protein Receptors

- Epinephrine binding activates $G_{\alpha s}$ by promoting GDP⇔GTP exchange.

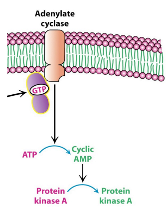


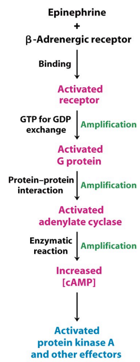






# G-Protein Receptors

- $G_{\alpha s}$ binds to activates Adenylate cyclase, which catalyzes the formation of the secondary messenger, cAMP.

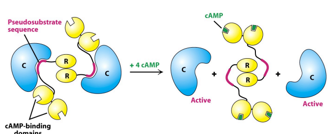


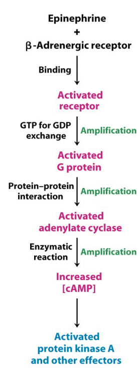






# G-Protein Receptors

- cAMP binds to the regulatory subunit of Protein Kinase A (PKA) and activates it.

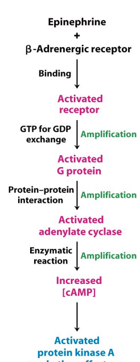




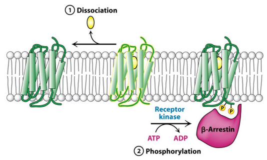

# G-Protein Receptors

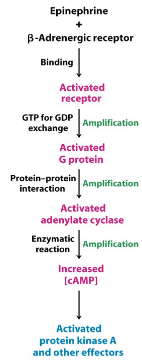
- PKA then phosphorylates and array of cellular proteins ( at Ser & Thr), which are leads to
  - Degradation of stored fuels
  - Secretion of acid by gastric mucosa
  - Dispersion of melanin granules
  - Opening of chloride channels



# G-Protein Receptors

- To turn off the pathway
  - $G_{\alpha s}$ catalyzes the hydrolysis of GTP back to GDP.
  - The β-adrenergic receptor can by inactivated by a G-protein receptor kinases (GRK2)






# G-Protein Receptors

- For other G-Protein receptors, it is the Gβγ subunits that are the activating entity
  - For example Acetylcholine/Potassium channel receptor.

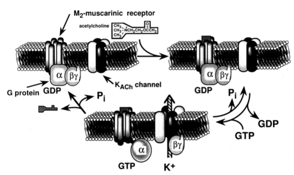
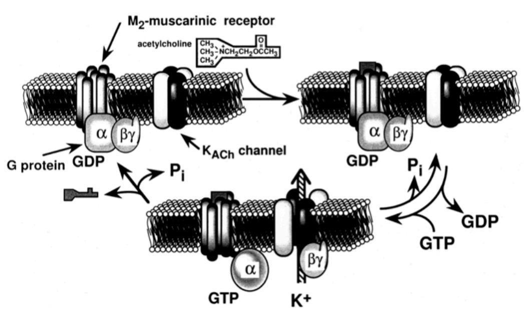



FIG. 2. Schematic representation of the G protein cycle involved in the activation of the muscarinic $K^+$ channel in response to acetylcholine.



# G-Protein Receptors

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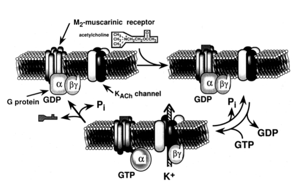

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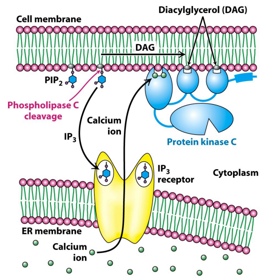
## The Phosphoinositide Cascade

- The phosphoinositide cascade also involved 7TM receptors that bind hormones.



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  - For example, the hormone angiotensin II binds to a 7TM receptor that activates a G-protein that in turn activates the enzyme phospholipase C
  - Phospholipase C produces the second messengers inositol 1,4,5-triphosphate ($IP_3$) and diacylglycerol (DAG)



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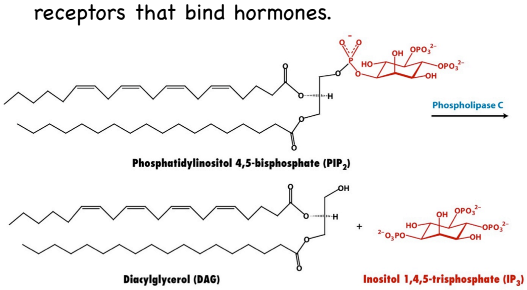




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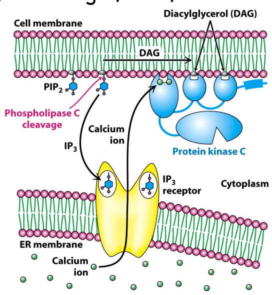
- $IP_3$ stimulates the release of yet another secondary messenger, $Ca^{2+}$, into the cytosol.



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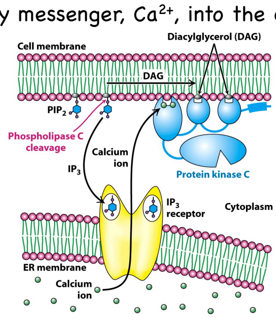




# $Ca^{2+}$ As a Secondary Messenger

- $Ca^{2+}$ is widely used as a secondary messenger.
  - It triggers muscle contraction
- $Ca^{2+}$ can also activate **Calmodulin-dependent protein kinases** (CaM kinases) by way of the regulatory protein **calmodulin**
  - This signaling is involved in
    - Fuel metabolism
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    - neurotransmitter synthesis and release.



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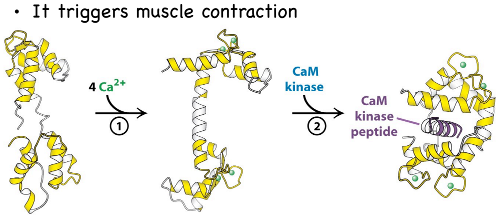


**Calmodulin (apo)**

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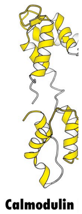


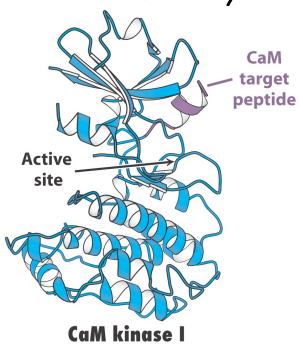


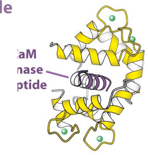



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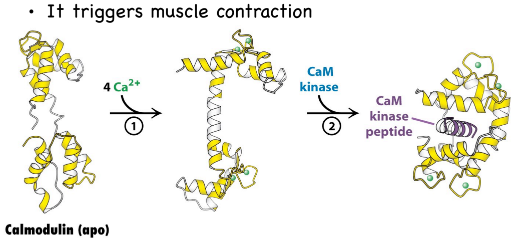




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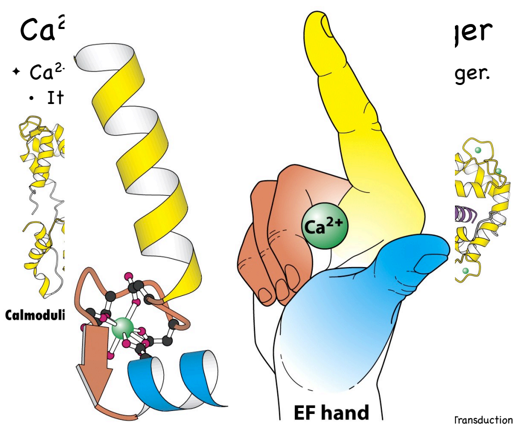




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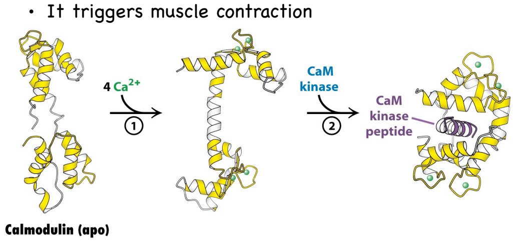

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## The Insulin Signaling Pathway

- The insulin signaling cascade involves a different type of receptor.
  - The tyrosine kinase receptor
  - The receptor itself is a protein kinase.
- Insulin is a protein hormone that simulates glucose uptake.
  - We will focus on the signal transduction pathway that leads to the mobilization of glucose transporters



## The Insulin Signaling Pathway

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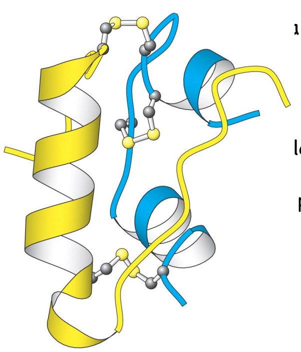



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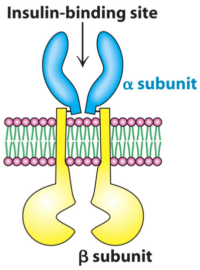
# The Insulin Signaling Pathway

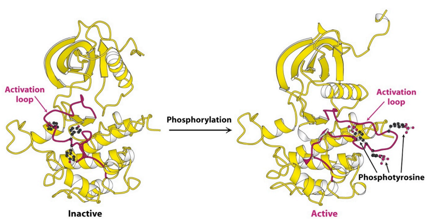
- The binding of insulin to its receptor activates a protein kinase activity within the receptor itself.






# The Insulin Signaling Pathway

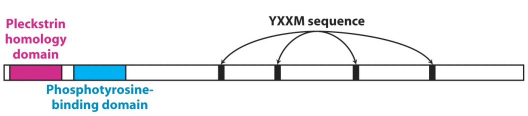
- The substrate for the kinase is the kinase itself.
  - Which in turn, is activated to phosphorylate other substrates






# The Insulin Signaling Pathway

- These other substrates include the **insulin receptor substrates** (IRS).



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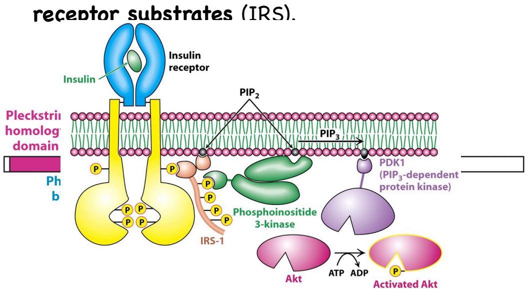

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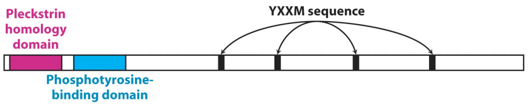
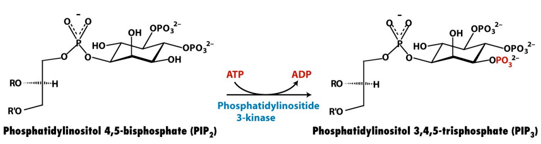





# The Insulin Signaling Pathway

- The phosphorylated IRS activates a phosphoinositide 3-kinase, which converts phosphotidyl inositol 4,5-bisphosphate ($PIP_2$) to phosphotidyl inositol 3,4,5-trisphosphate ($PIP_3$).



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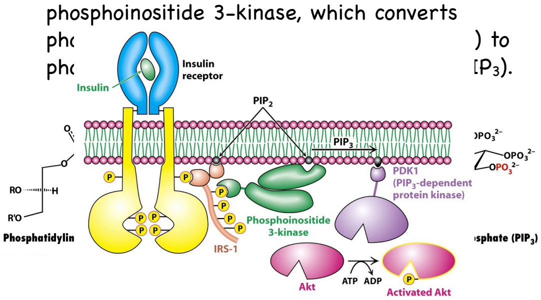




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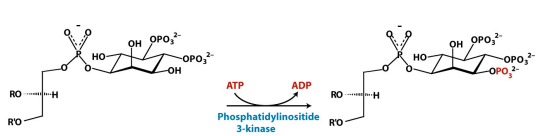
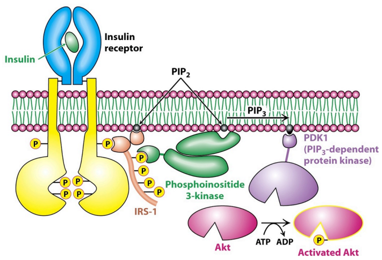


## The Insulin Signaling Pathway

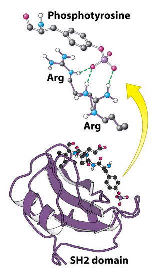
- The $PIP_3$ then activates a $PIP_3$-dependent protein kinase (PDK-1), which then phosphorylates and activates the Akt kinase.






## The Insulin Signaling Pathway

- The IRS has and example of the Src Homology 2 (SH2) domain, which bind to phosphorylated tyrosines.



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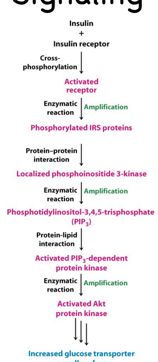




## Next up

- Lecture 10, Signal Transduction (con'd). (Chapter 14)