Chapter 14: Signal-transduction pathways

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I. Introduction { membrane protein

1. 發生生 metabolism 或 alter gene-expression pattern on sensing specific chemicals in its enviroment

2. Three examples

a. epinephrine : Kidney released. energy, improve cardiac function
energy-store mobilization

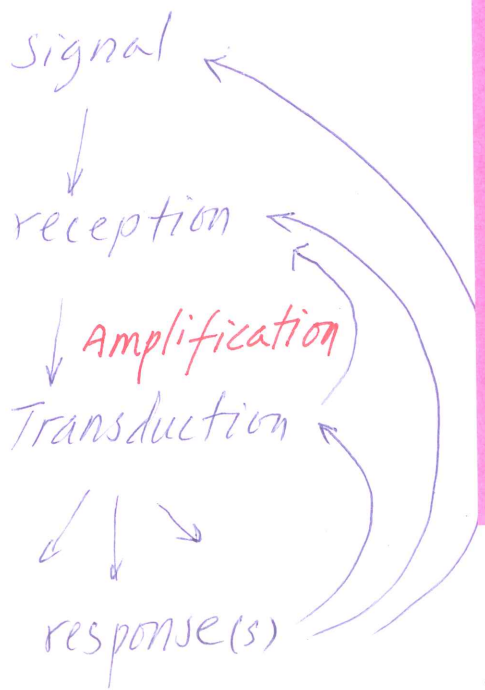
b. insulin: pancreas, uptake of glucose from bloodstream.
glucose uptake

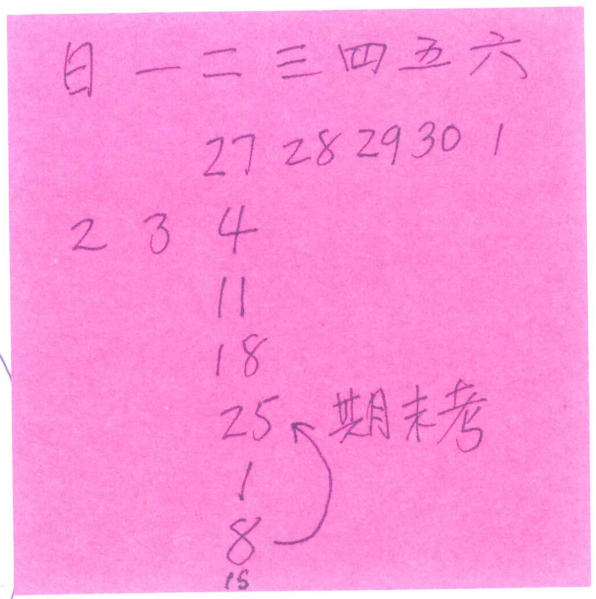
c. epidermal Growth factor (EGF): Wound response
Stimulate specific cell to grow & divide.
expression of growth-promoting gene

3. [certain molecule] ↑, chain reaction ⟶ physiological response

4.

II. Molecular circuit

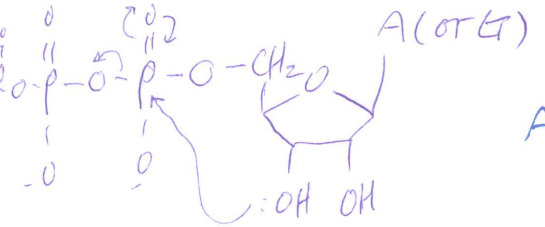




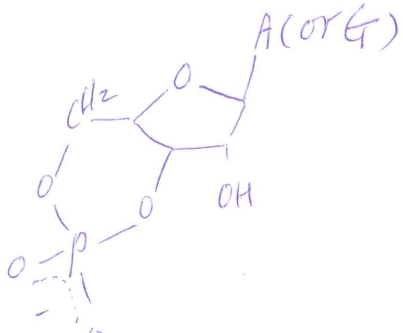
1. release of primary messenger

2. reception of " " :(extra & intracellar compartment) cause structural alter

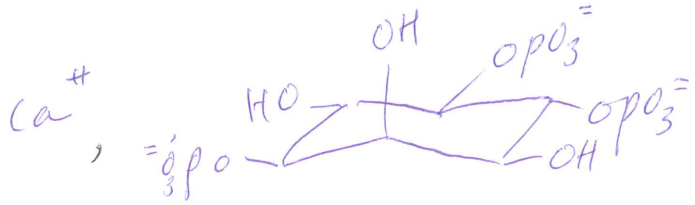
3. Delivery message inside the cell by second messenger
   Amplification
   diffuse through cell compartment



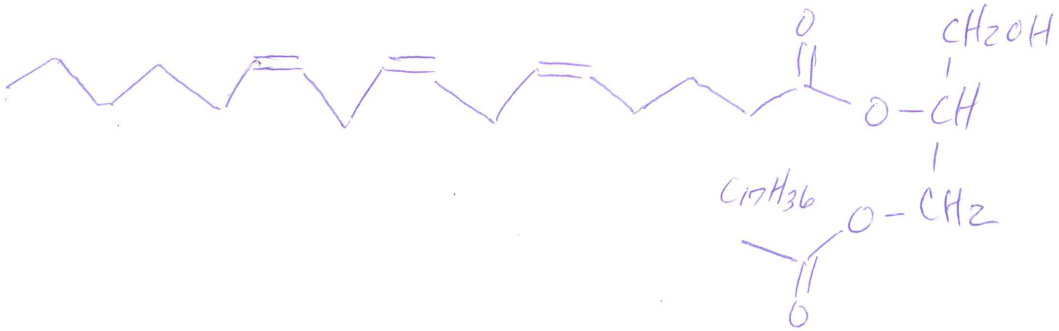
ATP



cAMP, cGMP



inositol 1.4.5-triphosphate (IP_3)

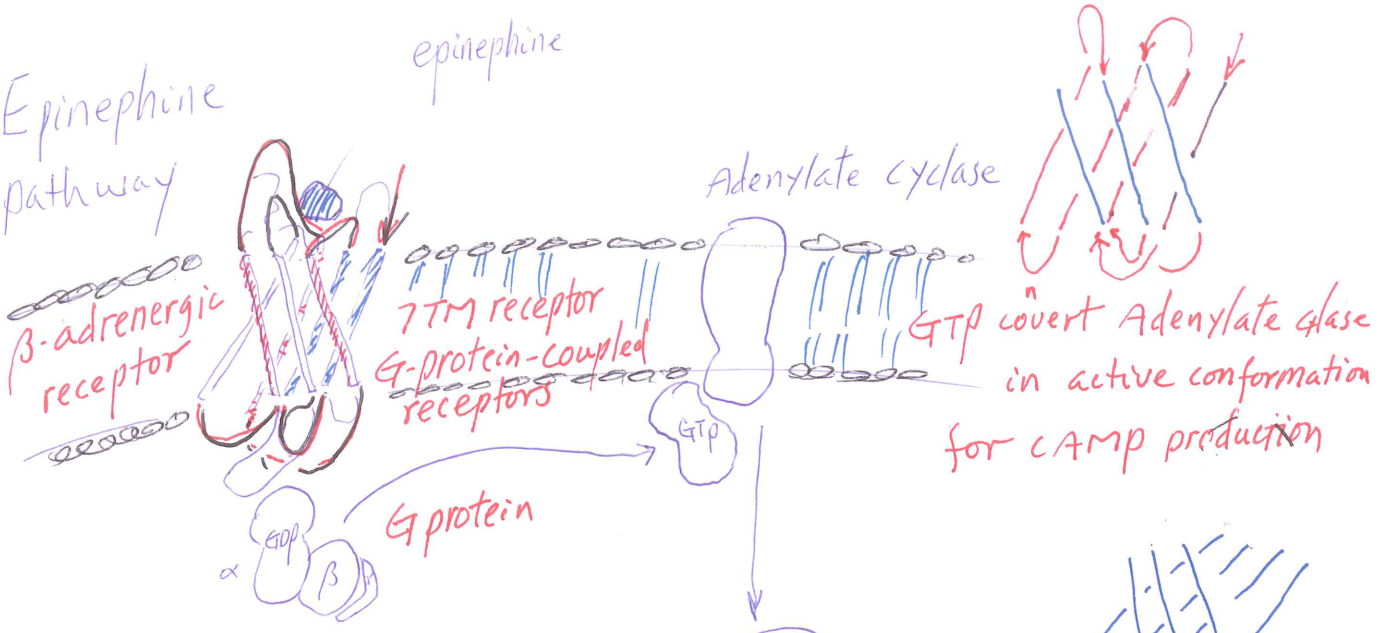


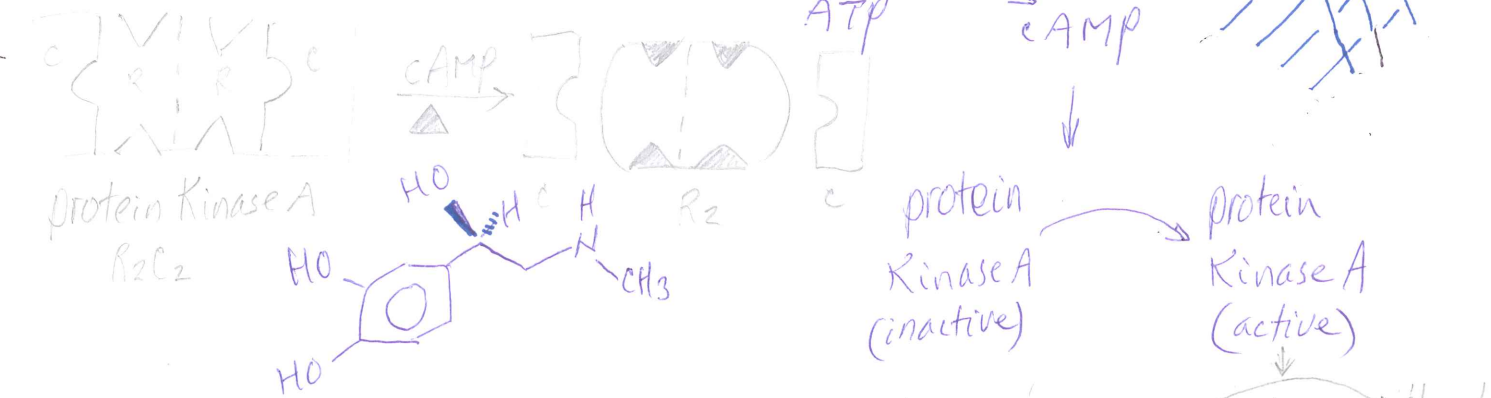
Diacylglycerol (DAG)

4. Activation of Effectors that directly alter physiological response

5. Termination of Signal

III Epinephine pathway





epinephine

↓

β-adrenergic receptor

(7 TM) receptor

Binding ↓

Activated receptor

GTP ⇌ GDP exchange ↓ Amplification

Activated G protein

protein-protein interaction ↓ Amplification

Activated Adenylate cyclase

Enzymatic rxn ↓ Amplification

Increase [cAMP]

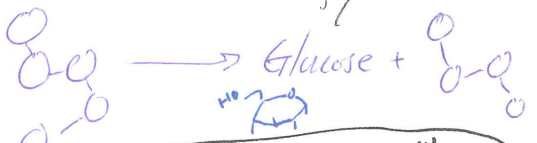
↓

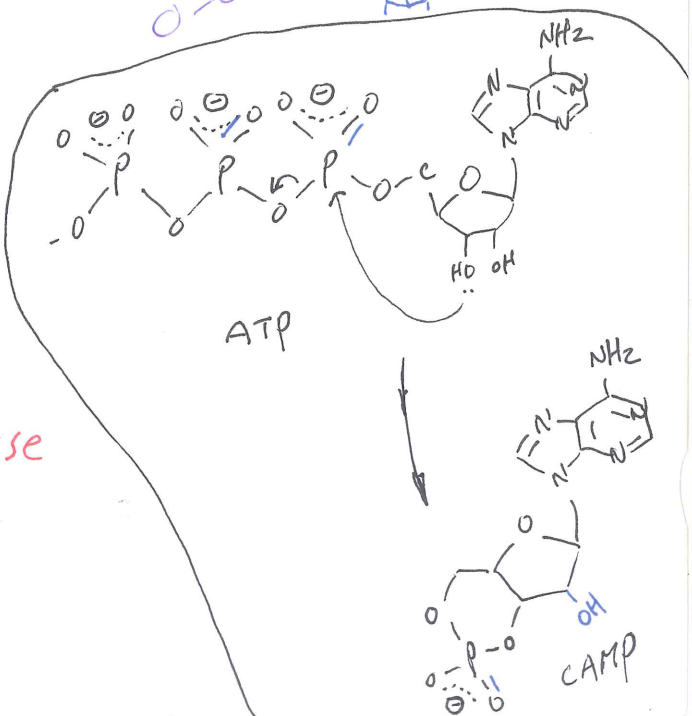
Activate protein Kinase A

phosphorylase b Inactive → phosphorylase a active

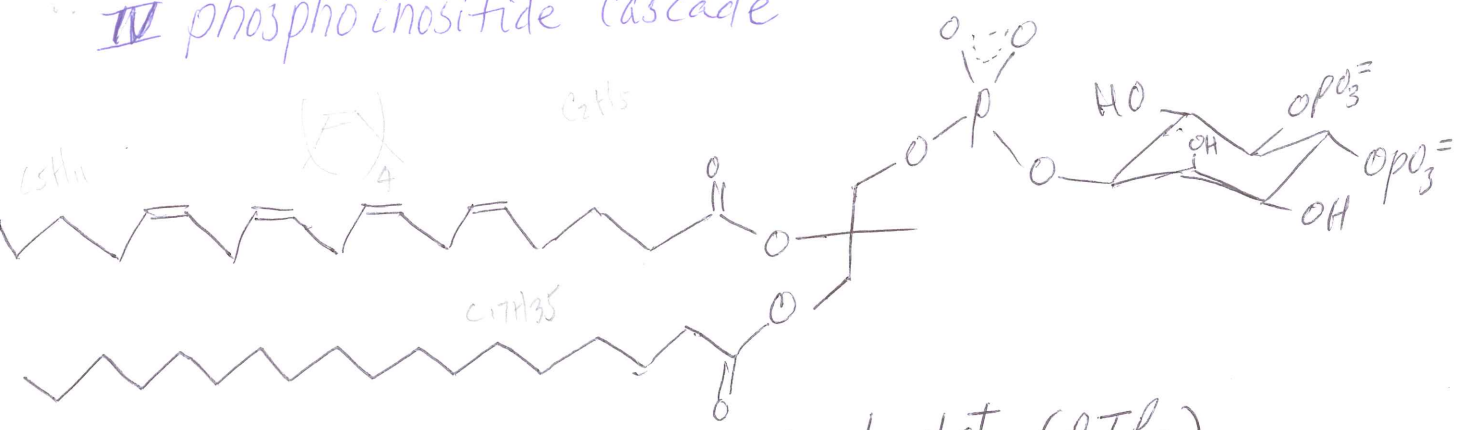
release Glucose

(Glycogen breakdown)



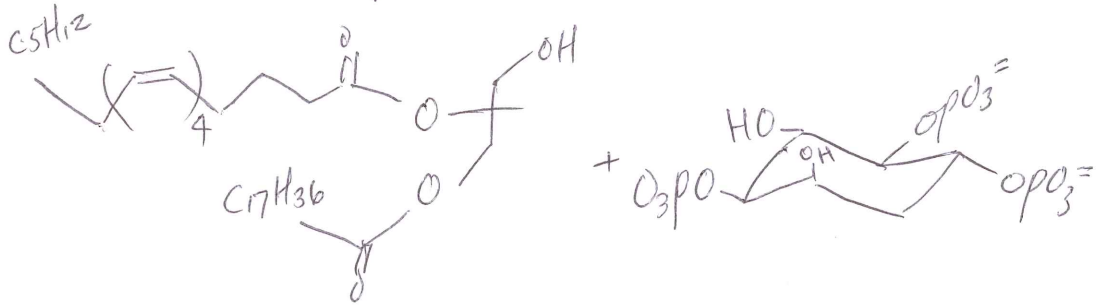


IV phosphoinositide cascade

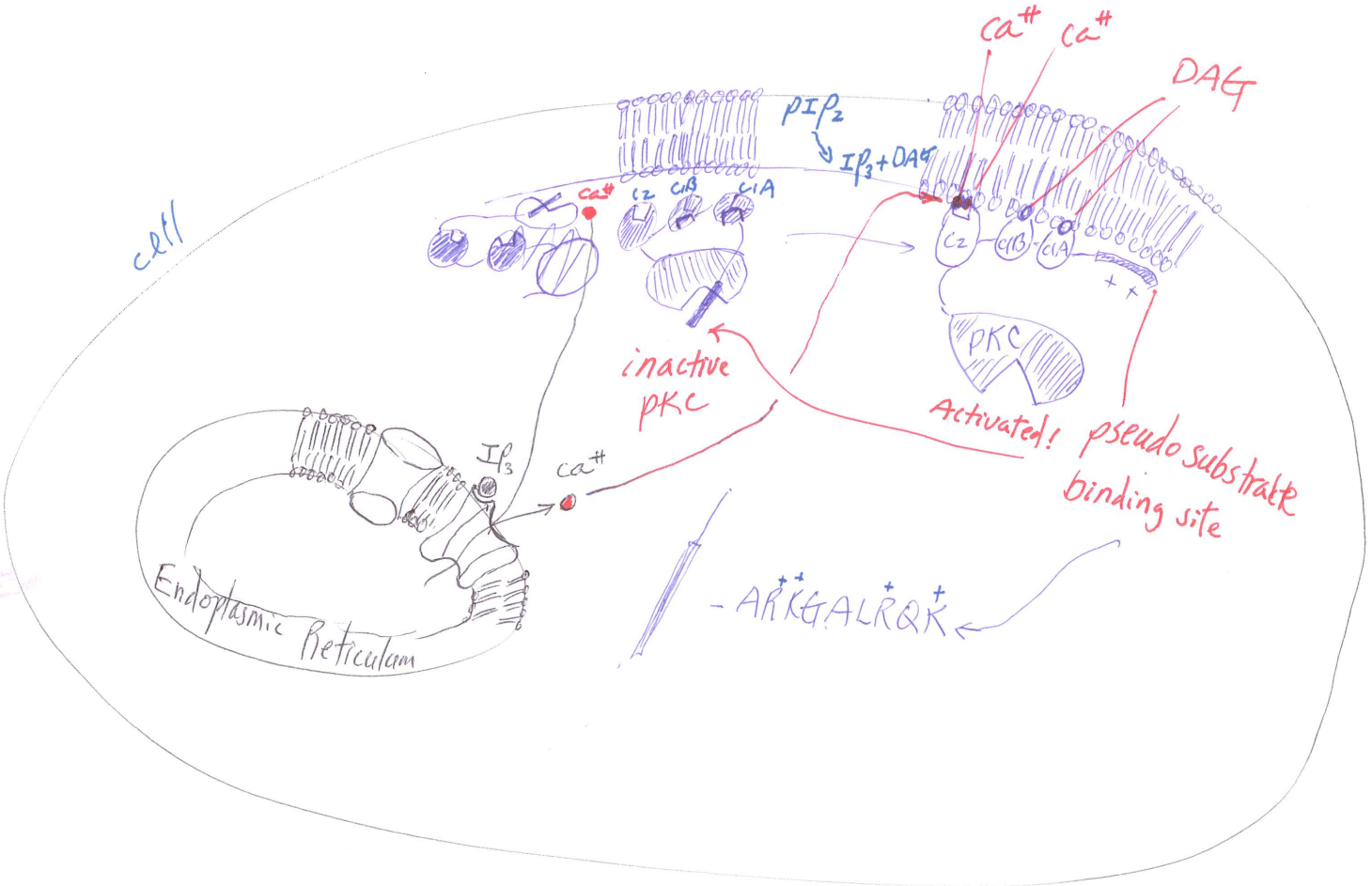


phosphatidylinositol 4.5-bisphosphate (PIP_2)

↓ phopholipase C



Diacylglycerol (DAG) Inositol 1.4.5 triphosphate (IP_3)



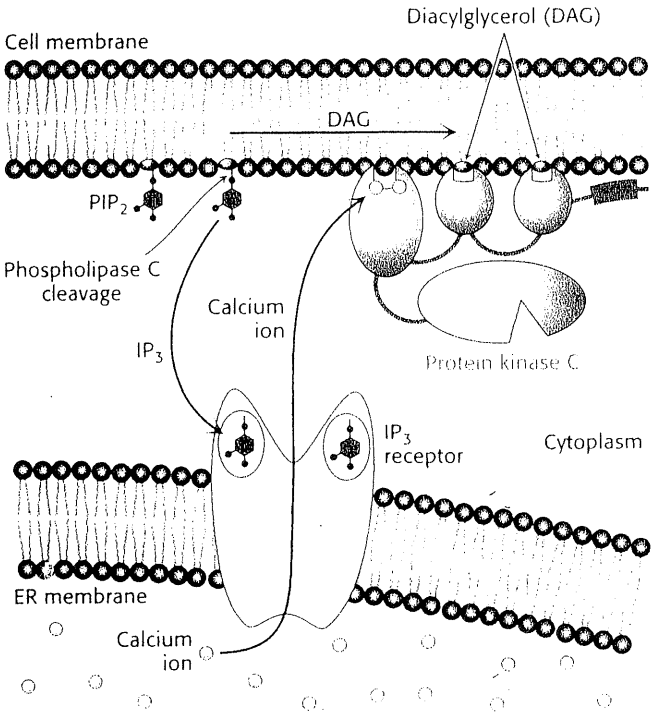


Figure 14.12 Phosphoinositide cascade. The cleavage of phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) results in the release of calcium ions (due to the opening of the IP_3 receptor ion channels) and the activation of protein kinase C (due to the binding of protein kinase C to free DAG in the membrane). Calcium ions bind to protein kinase C and help facilitate its activation.

this kinase require bound calcium to bind to DAG. Note that diacylglycerol and IP_3 work in tandem: IP_3 increases the Ca^{2+} concentration, and Ca^{2+} facilitates the activation of protein kinase C. The phosphoinositide cascade is summarized in Figure 14.12. Both IP_3 and DAG act transiently because they are converted into other species by phosphorylation or other processes.

branched pathway is quite complex; so we will focus solely on the major

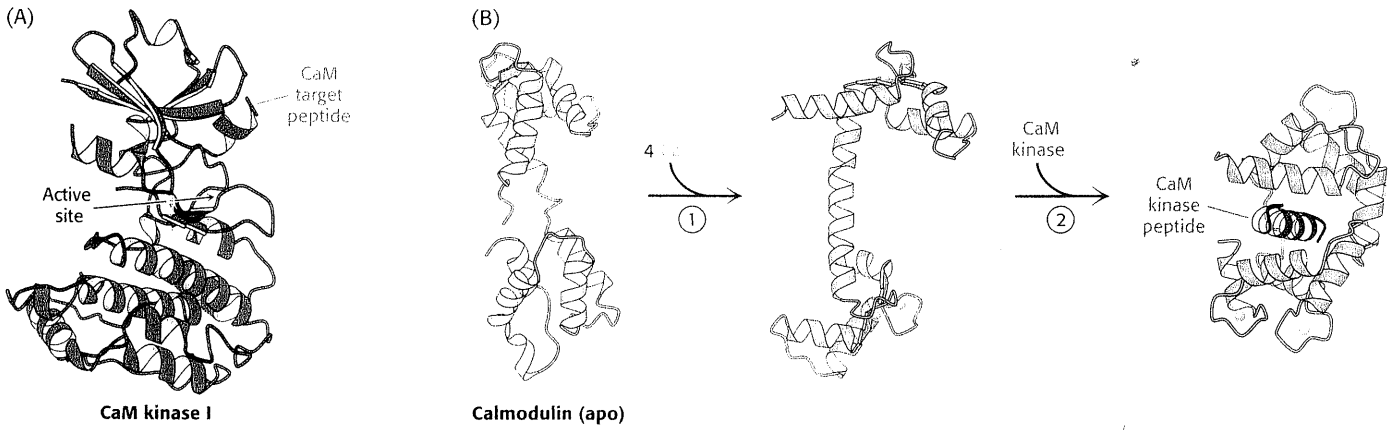
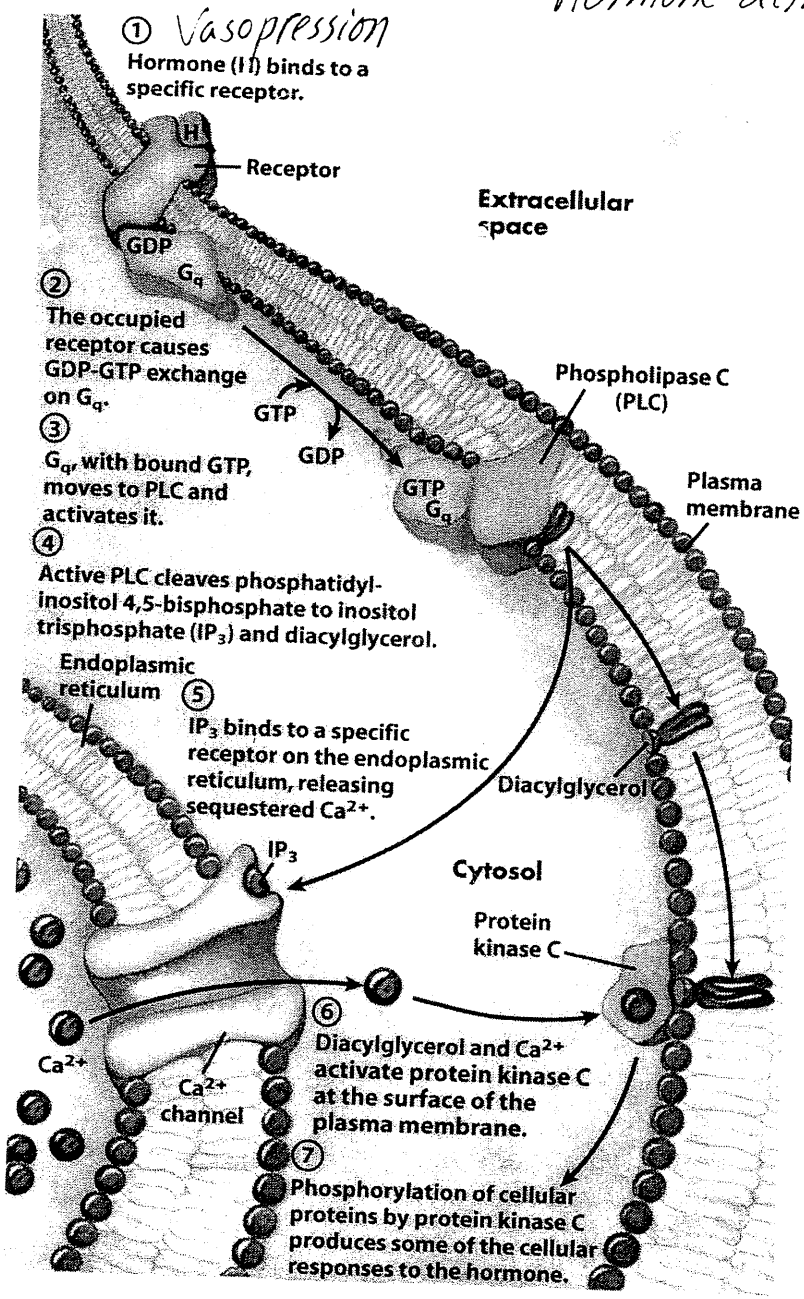
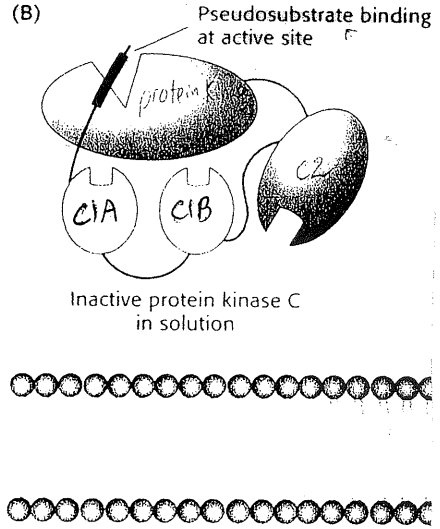
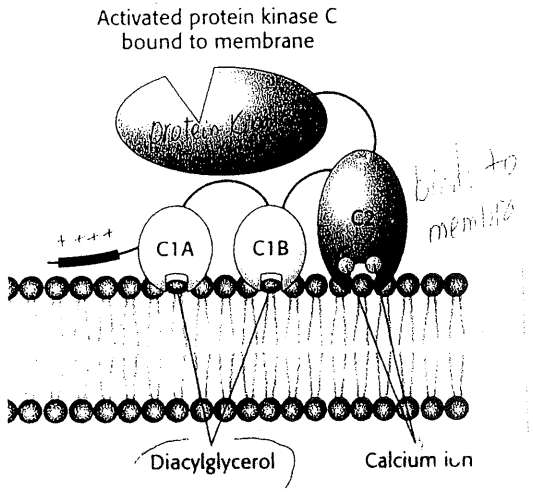


Figure 14.16 Calmodulin binds to α helices. (A) An α helix (purple) in CaM kinase I is a target for calmodulin. (B) After Ca^{2+} binding (1), the two halves of calmodulin clamp down around the target helix (2), binding it through hydrophobic and ionic interactions. In CaM kinase I, this interaction allows the enzyme to adopt an active conformation. [Drawn from 1A06, 1CFD, 1CLL, and 1CM1.pdb.]

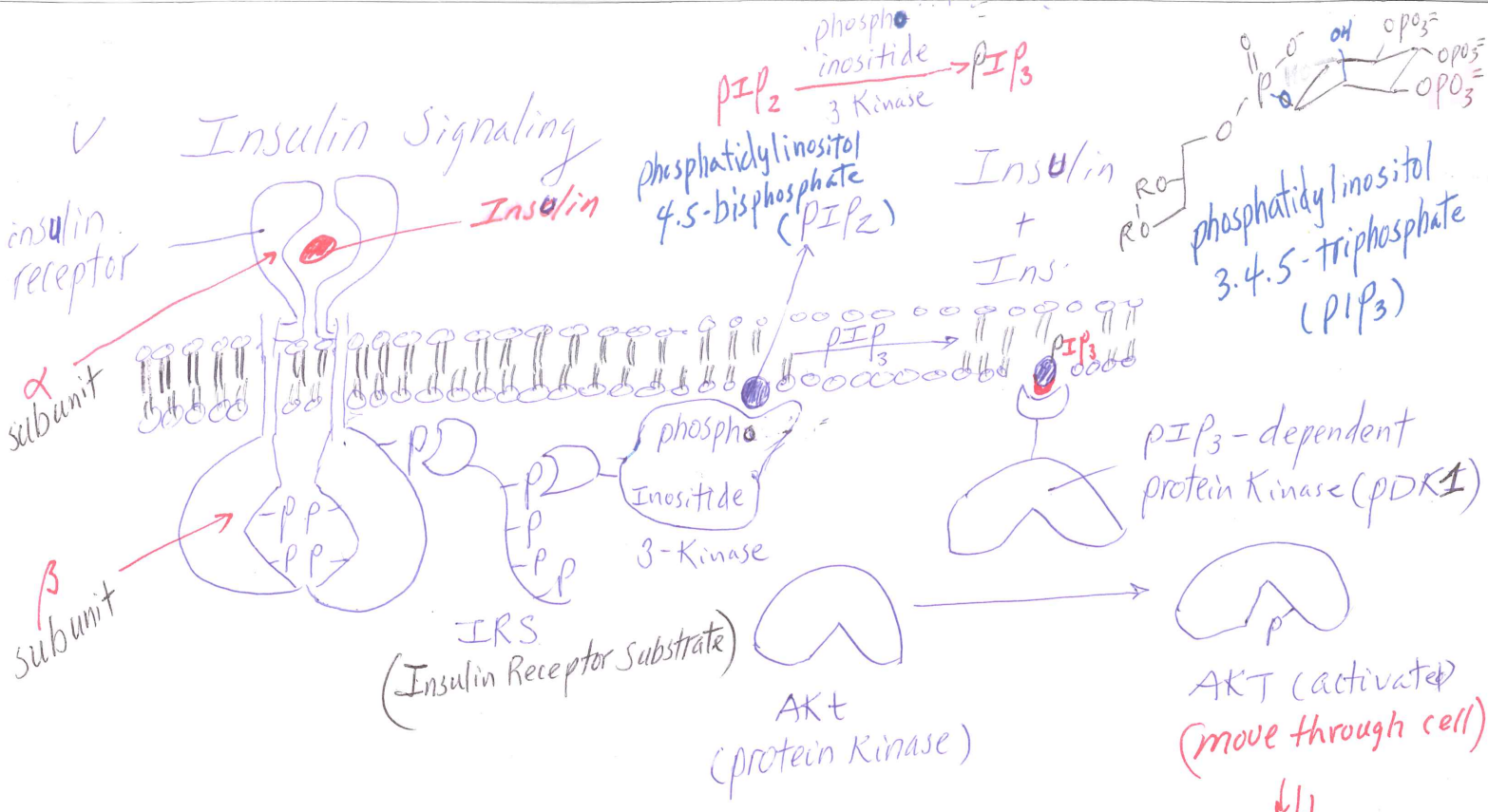
Hormone-activated phospholipase C & IP_3





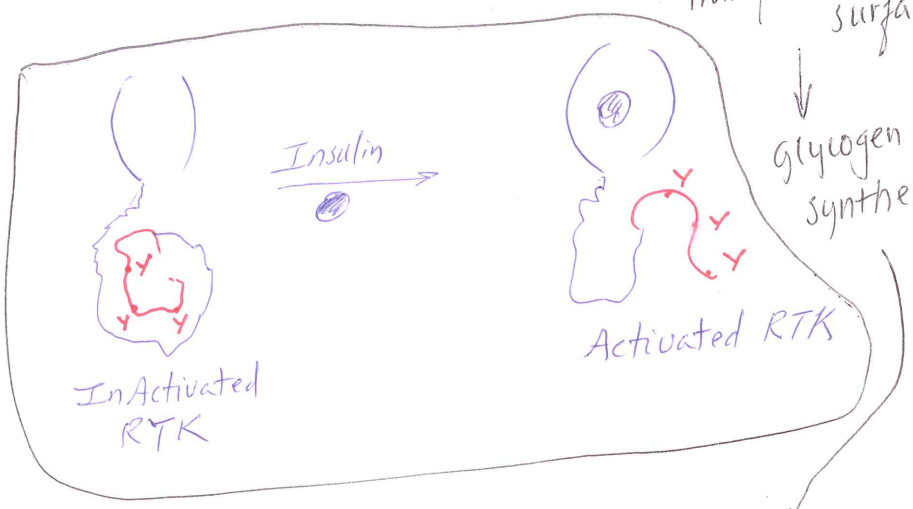


Insulin Signaling



Increased glucose transporter on cell surface

glycogen synthesis



Insulin + Insolin Receptor

cross-phosphorylatn

Activated Receptor

Enzymetic rxn | Amplification

phosphorylated IRS

protein-protein interactn

Localized phospho~~tidyl inositide~~ inositide 3-Kinase

enzymatic rexn | Amplification

PIP3

protein-lipid interaction

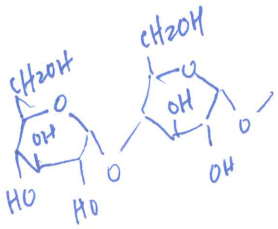
Activated PIP3-dependent protein Kinase

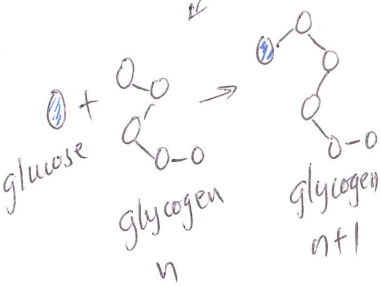
Enzymatic rxn → Amplification

Activated Akt protein Kinase

→ increased Glucose transporter on cell Surface

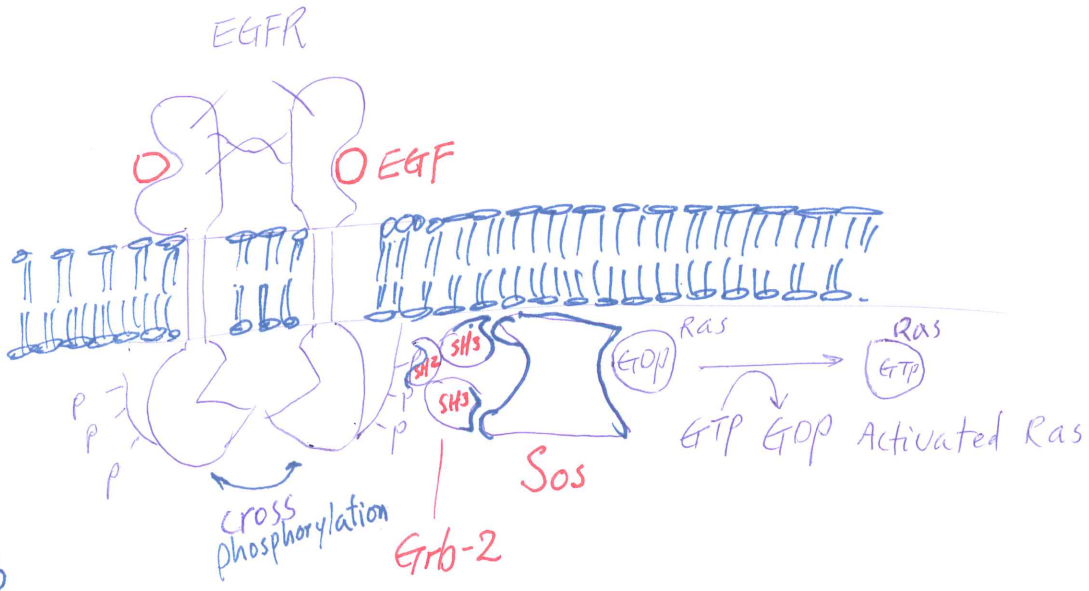
→ Glycogen Synthesis





VI. EGF (epidermal growth factor) Signaling

與 Insulin Receptor 不同之處是 IR 為分子間双硫鍵所形成的 dimer，而 EGFR 唯有在與 EGF 結合時，才形成 dimer



T.S

Epidermal growth factor
+
EGFR

cross phosphorylation ↓

phosphorylated receptor

prot-protein interaction ↓

EGFR-Sos Complex

GTP ⇌ GDP ↓

Activated Ras

prot-protein interaction ↓

Activated Raf

Enzymetic rxn ↓

Activated MEK —enzymetic rxn→ Activated ERK

Activated ERK —enzymatic rxn→ phosphorylated transcription factors (Fos, Jun)

phosphorylated transcription factors (Fos, Jun) —Nuclei→ active transcription factor (Jun, Fos)

active transcription factor (Jun, Fos) → 加速 gene 之 replication, transcription

加速 gene 之 replication, transcription → cell divided, proliferate & growth