



The Phosphoinositide Cascade

- Used by many hormones (e.g. ADH)
- Binding of a hormone to 7TM receptor

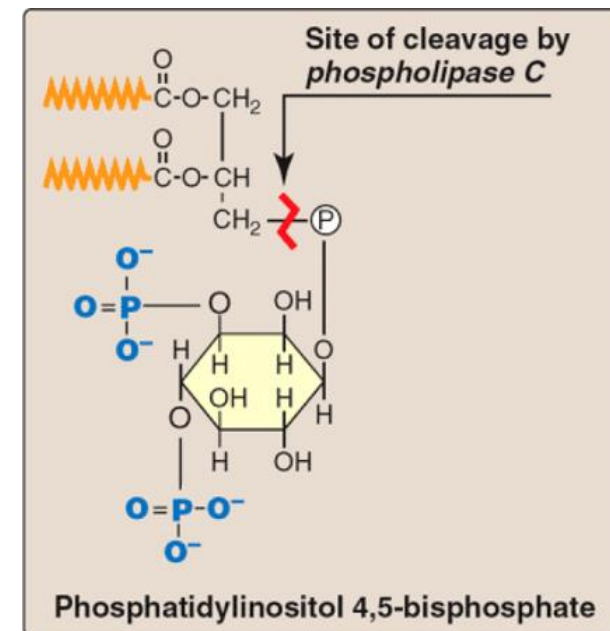
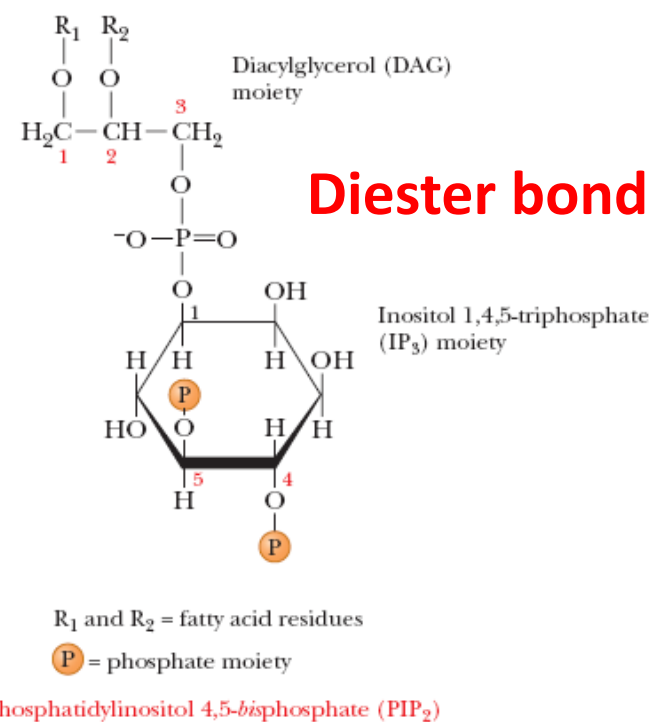
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Activation of G Protein

↓

Activation of Phospholipase C
(many isoforms) – PIP₂

- Two messengers are produced
 - Inositol 1,4,5-trisphosphate, hydrophilic, (Soluble)
 - IP₃ is the actual second messenger
 - Diacylglycerol, amphipathic (membrane)

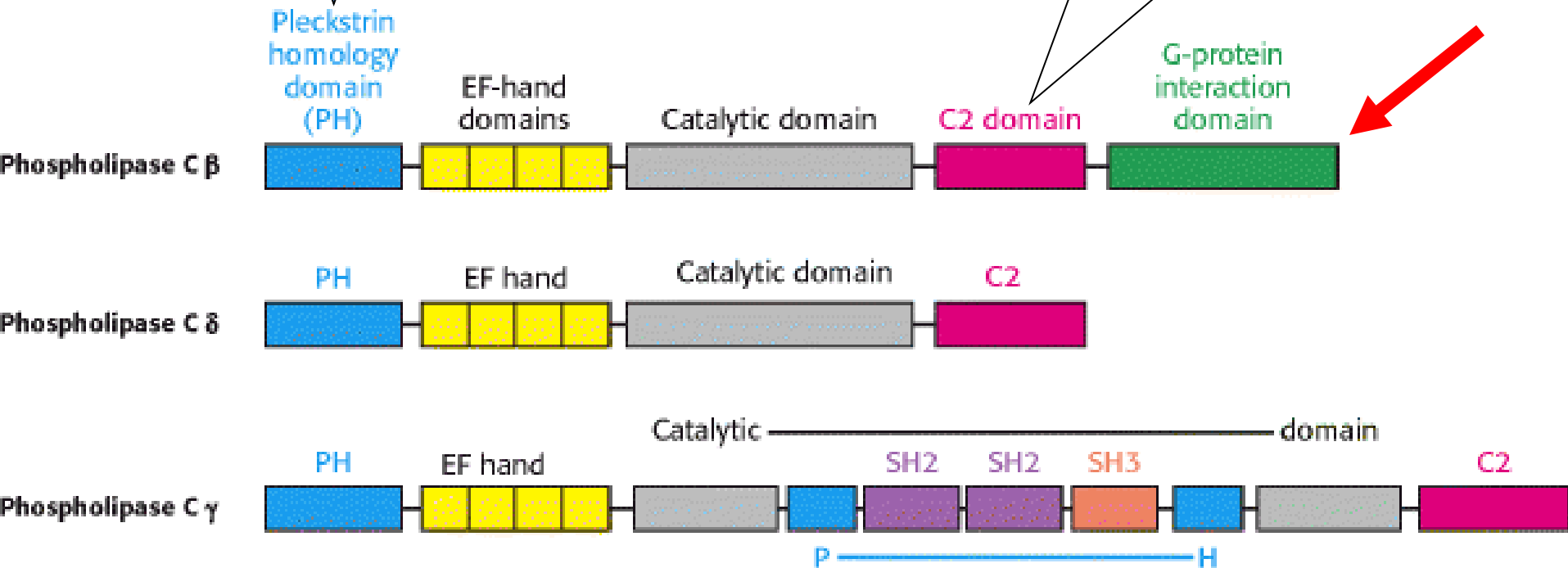




The domain structures of three isoforms of Phospholipase C

Binds a lipid head group

Binds phospholipid head group



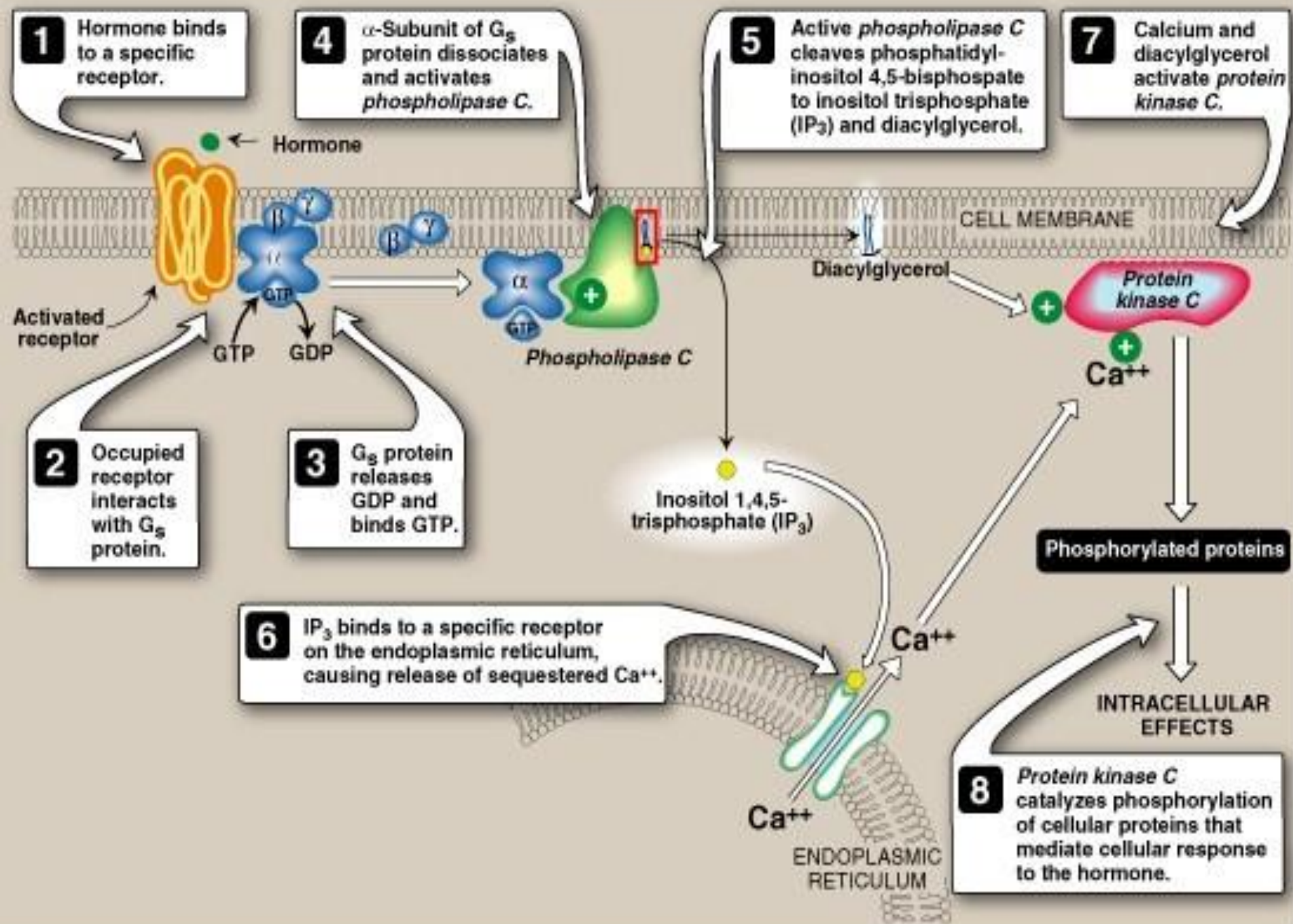


Binding of a G protein brings the enzyme into a catalytically active form

Membrane

G
Protein







Effects of Second Messengers

Inositol trisphosphate (IP3)

- ✓ Opens Calcium Channels
- ✓ Binding to IP₃-gated Channel
- ✓ Cooperative binding (sigmoidal)

Diacylglycerol (DAG)

- ✓ Activates Protein Kinase C
- ✓ Ca²⁺ is required
- ✓ Phosphorylation of many target proteins



The domain structures of protein kinase C isoforms

Binds
Diacylglycerol

Interaction with
phospholipids

Pseudo-
substrate

C1A

C1B

C2

Protein kinase

Protein kinase C α , β , γ



Pseudo-
substrate

C2

C1A

C1B

Protein kinase

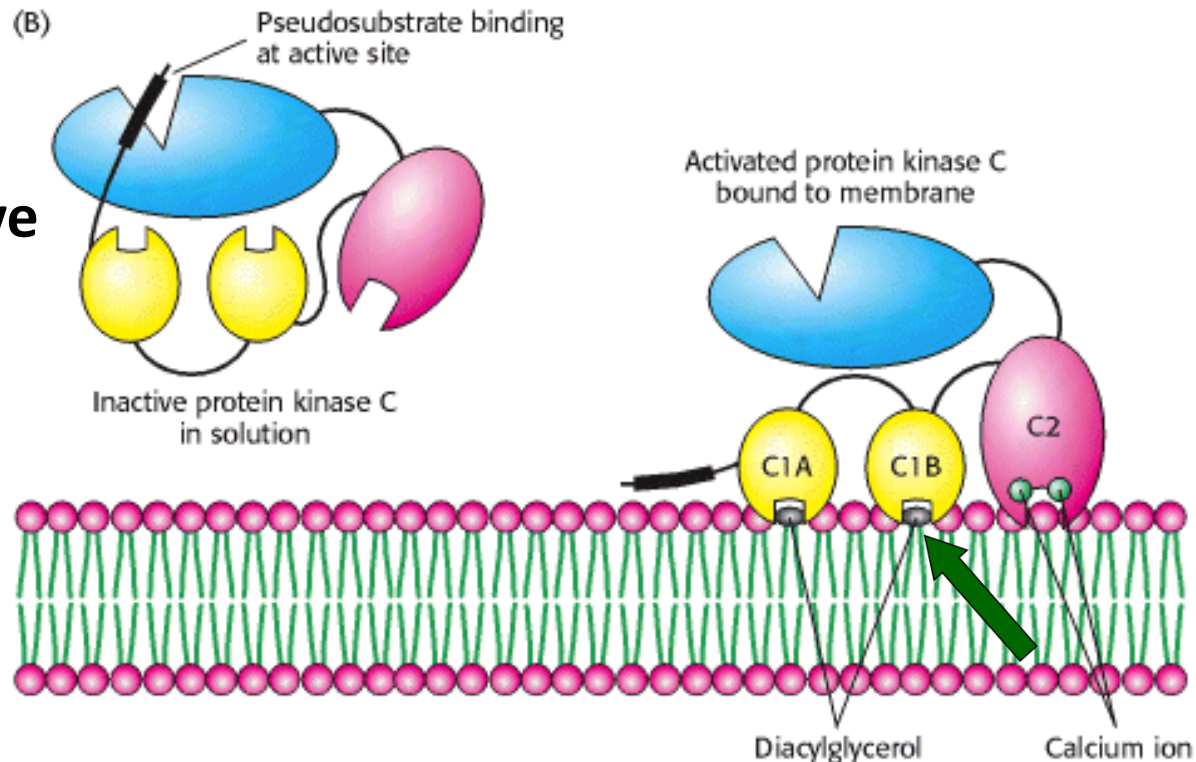
Protein kinase C δ , ϵ , θ , η





Pseudosubstrate Sequence

Competitive Inhibitor



- Resembles the substrate sequence: A-R-K-G-**A**-L-R-Q-K
- Substrate Sequence: X-R-X-X-(**S,T**)-Hyd-R-X
- Binds to the Enzyme's Active Site



Termination of IP₃ Signal

IP₃ is a Short-Lived Messenger

Lithium Ions,
Used to treat
some
psychological
disorders
Inhibits IP₃
recycling

