Lecture 10 Cell communication Part one

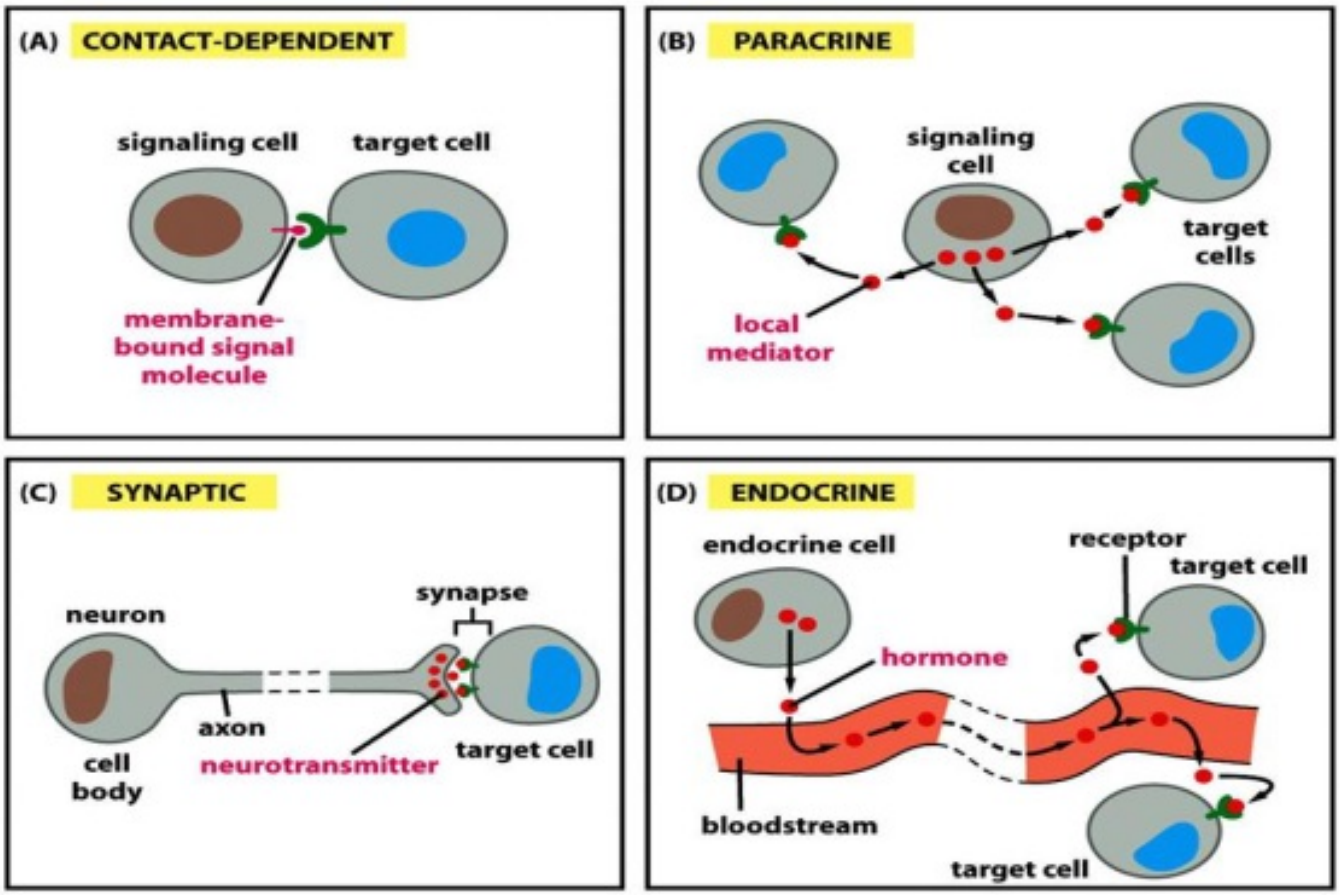
Quarum sensing in bacteria(群体感应现象) A Nice video to introduce anglerfish

1. Overview of cell communication

- CELL-SURFACE receptors
- INTRACELLUAR receptors

> What is the difference between ligand and receptor?

Here are Cell-Cell contact, Synaptic (fast), Paracrine(旁分泌)/autorine 自分泌 (local environment)，endocrine 内分泌（long distance）



Effects in siganling can be fast and slow. Protein synthesis is slow, but protein behavior is fast. The same singals trigger different effects, which include same signal in different receptors, same signal and receport but different effector, same singal but vary concentration(morphogen).

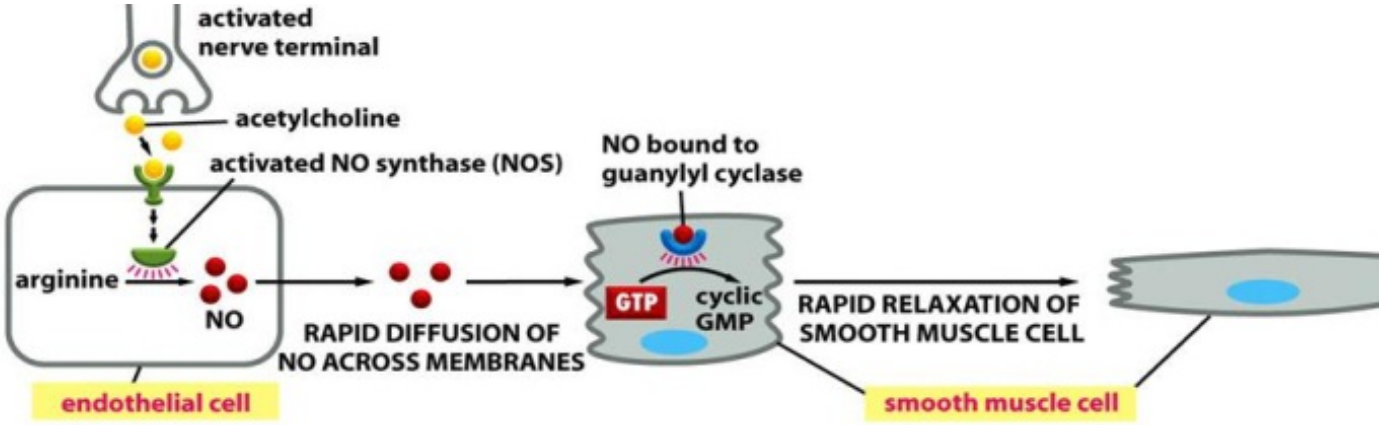
Cell is programed to respoond to specific combinations of signals. If deprived of appropritate survival signals, a cell will undergo a form of cell suicide known as apoptsisi.

To ensure quicker response, many proteins in signaling have short half lives, which have faster turn over rate react.

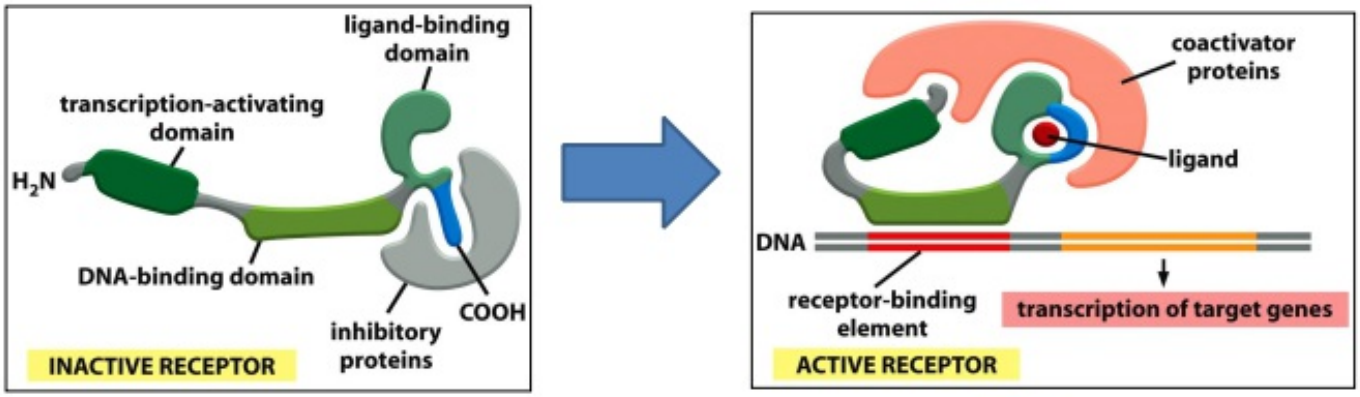
2. Intracelluar receptors

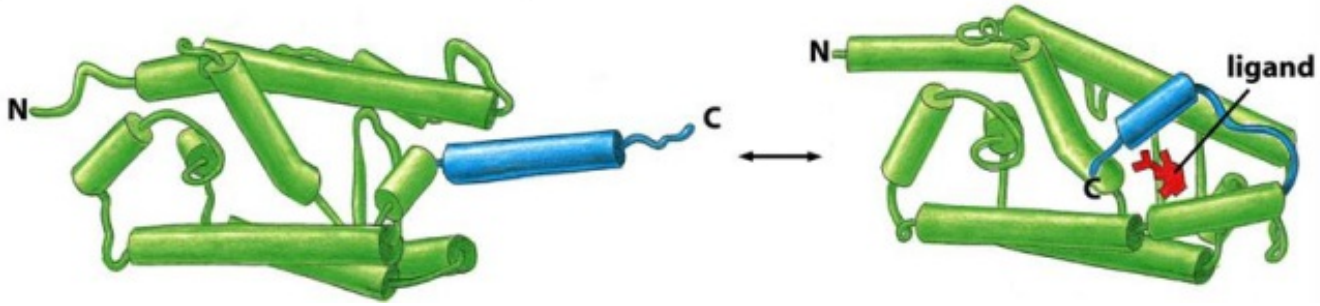
Sigaling of NO in smooth muscle can relaxate blood vessel. NO's half life is 5-10 sec, which convert salt by water and O2. So nitroglycerin is used to treat angina pectoris 心绞痛, which increase cGMP to diate of blood vessel. And Viagra

(Sildenafil) can inhibite cGMP degradation.



Singaling via nuclear receptor. Here are steroid hormones, Thyroid hormone, Retinoids 维生素A。Nuclear receptors work either as homodimer or heterodimer. Serve both as ligand receptor and gene transcription factor. Hormone receptors can trgger both primary and secondary responses.



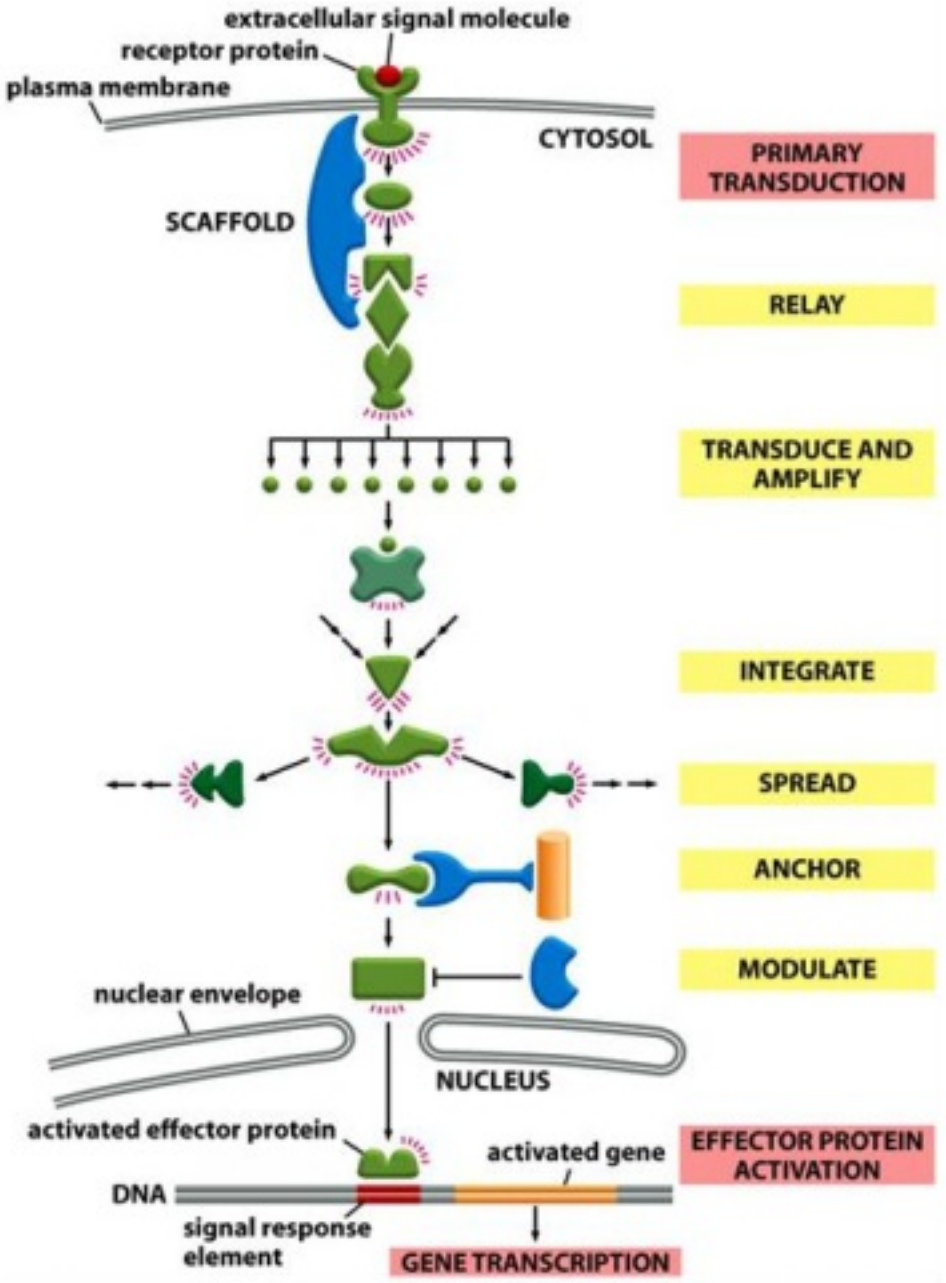


3. General principles of cell surface signaling

These are three major classes of cell surface receports, ino-channel-coupled receptors, G-Protein-Coupled Receport, Enyzme-Couple Receport.

The first messenger is extracellular singals. And the second messenger is small molecules generated in larger number after receptor activation. Thery are either hydrophilic or lipid diffusing, which work on effector proteins and relay signals. Such as, cAMP, cGMP, Ca2+, diacylglycerol(DAG 甘油二酯), Inositol triphosphate(IP3 肌醇三磷酸)。

Intracellular singaling proteins can: **relay** signals to the next compont, act as a **scaffold** to bring two signaling proteins more quickly and efficiently, **transform** the signal into a different form, **Amply** the signal it receives---signal cascade 瀑布, **Integrate** signals from two or more pathways, Spread signals from one pathway to another--**crosstalk**, **Anchor** signaling proteins to a specific structure. **Modulate** the activity of signaling proteins.



Protein phosphorylation, GTP-binding, cAMP or Ca2+ binding, Ubiquitination are important types of switch to regulate protein activity.

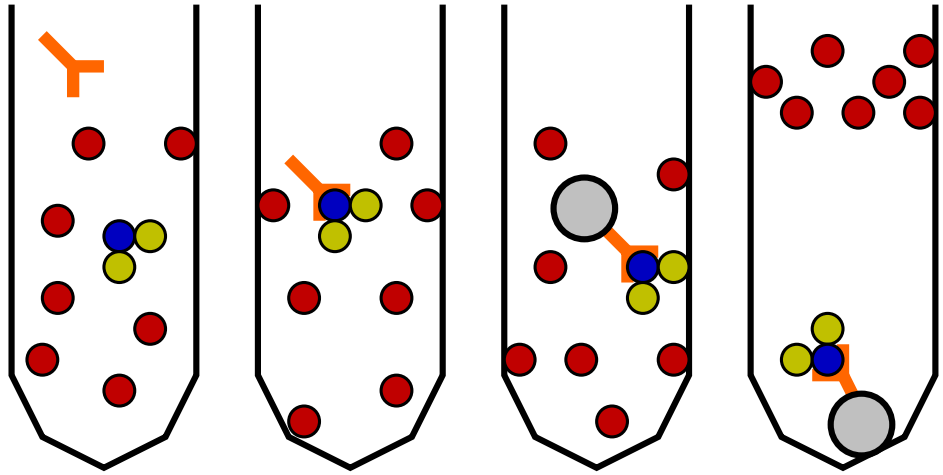
Protein phosphorylation is one major way of post-translational modification to regulate protein activity. Here are two categories: Serine/Threonine kinase and Tyrosine kinase. Protein kinases are major therapeutic targets in human diseases. Signaling protein itself is a kinase which can phosphorylate and activate downstream effectors---Phosphorylation cascade.

GTP-binding proteins(G-proteins)

To achieve high speed and specificity in signaling.

- Preformed signaling complex on a scaffold protein.
- Assembly of signaling complex on an activated receptor.
- Assembly of signaling complex on phosphoinositide docking sites.

4. Several methods to study cell signaling



1. Researcher adds antibody.
2. Antibody binds target.
3. Protein A beads bind antibody.
4. Centrifugation sediments beads.

Protein co-immunoprecipitation can be used to receptor-ligand interaction, kinase-substrate interaction and other protein interaction partners.

Western Block

In vitro protein activity assay.

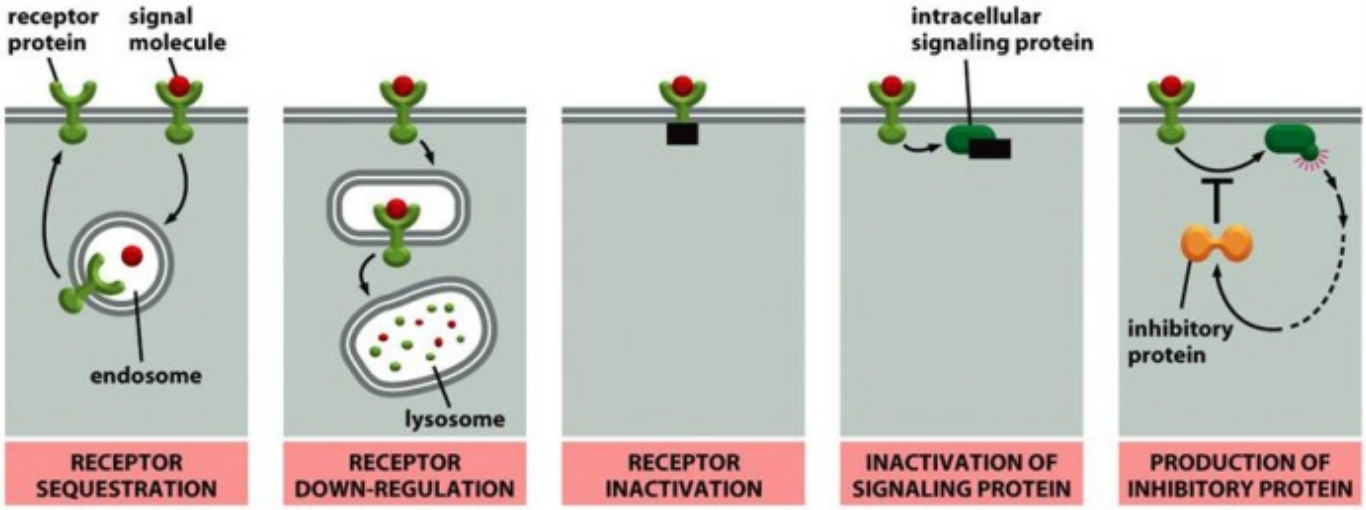
shRNA/siRNA, inhibitors work by triggering target mRNA degration.

Rescue assay is used to locate signaling protein on upstream or downstream.

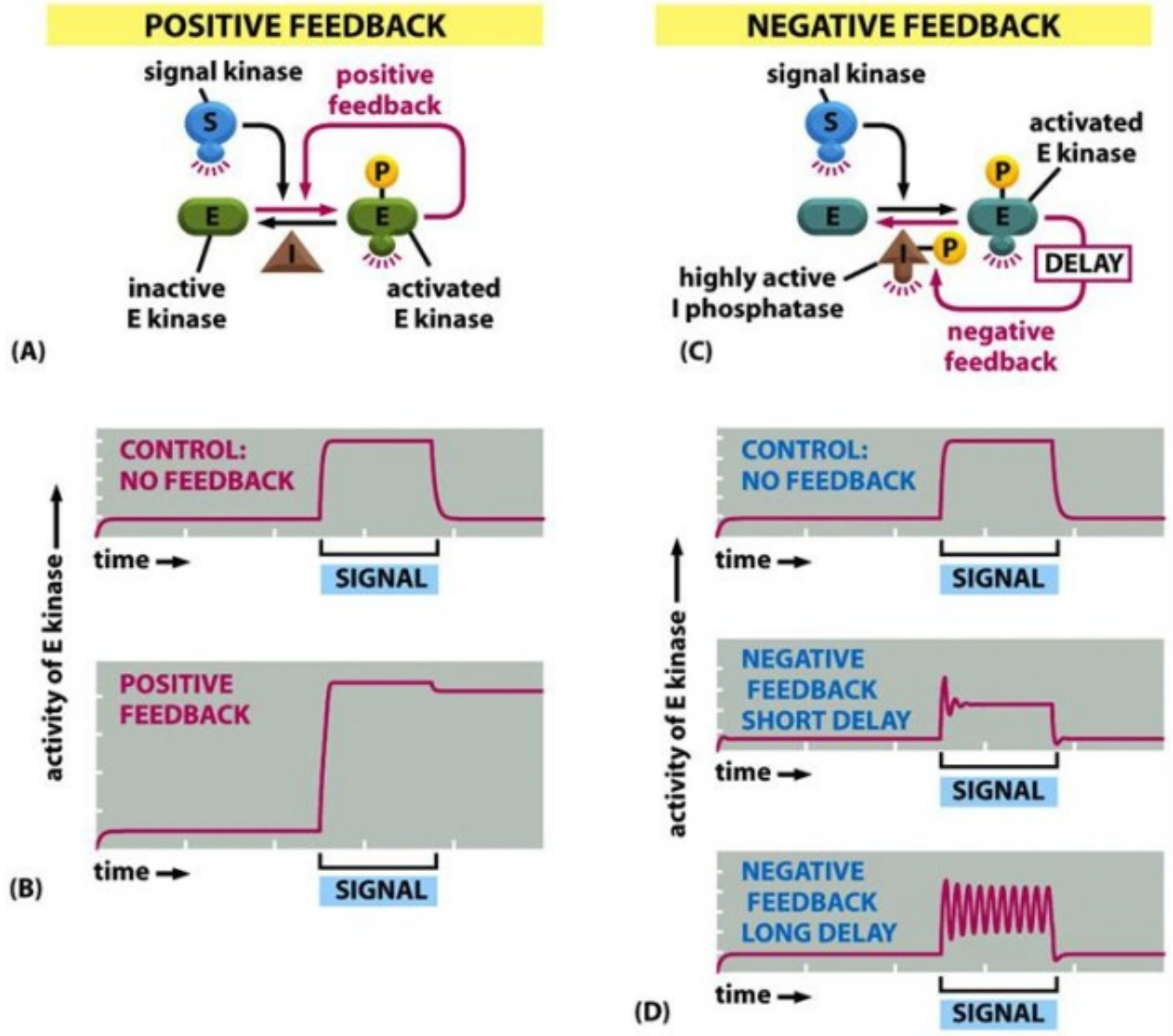
5. Positive and negative feedback in signaling and signaling kinetics

Switchlike responses could be due to cooperative response, or concerted effect of a simultaneous inhibition for the opposite reaction. Positive feedback can give switchlike response.

Negative feedback allows adaptation/desensitization 脱敏 for cells.


receptor protein
signal molecule
endosome
lysosome
intracellular signaling protein
inhibitory protein
RECEPTOR SEQUESTRATION
RECEPTOR DOWN-REGULATION
RECEPTOR INACTIVATION
INACTIVATION OF SIGNALING PROTEIN
PRODUCTION OF INHIBITORY PROTEIN

Sea


POSITIVE FEEDBACK
signal kinase
positive feedback
S
P
E
E
I
inactive E kinase
activated E kinase
(A)
NEGATIVE FEEDBACK
signal kinase
activated E kinase
highly active I phosphatase
DELAY
negative feedback
(C)
activity of E kinase
CONTROL: NO FEEDBACK
time
SIGNAL
POSITIVE FEEDBACK
(B)
NEGATIVE FEEDBACK SHORT DELAY
NEGATIVE FEEDBACK LONG DELAY
(D)