

Chapter 12 -lite

Biosignaling

Problems: Read chapter on your own and be able to describe one system

12.0 Introduction

Last chapter found that cell was bounded by impermeable membrane that ions and polar compounds can't pass so the cell interior would seem to be pretty much isolated. Then learned about membrane proteins that allow things to get through membrane, so the inside and the outside of the cell could pass molecules into or out of the cell. Now put into the more complex biological context. Even a cell as simple as an E coli needs to obtain information about its environment so it can move toward or away from food, oxygen, light heat, competitors, noxious substances etc. A multicellular organism is even more complex. A Cell has to interact with all the cells around it, and respond to signals from nerves and hormones washing around it. This is all done in a myriad of different ways by proteins on the cell surface. This chapter serves as an introduction, a survey of some of the hundreds of ways cells interact with each other. We won't have time to study this chapter in depth, but hopefully this will get you started so when you need more information you will have a place to get started.

12.1 General Features of Signal Transduction

Specificity - Ideally a unique molecule will bind to it's own unique receptor and elicit a single response from a cell.

All based on Protein-Small molecule interactions that studied back in Chapter 6. A large number of weak, non-covalent interactions are used to bind a molecules to its receptor protein. The receptor protein then changes conformation and this is the start of the cell's response.

Additional specificity in multicellular organisms because most of the time only a few cells in the entire organism have the proper receptor to respond to a given stimulus

Even different cells within a single organism may respond differently to the same stimulus, depending on the tissue where the cell is found.

Amplification due to:

High affinity

Typical K_D of receptor-ligand is 10^{-10} M (picomolar)

Get from plots similar to those we did for enzymes

Called Scatchard Analysis (See page 421- Box 12-1)

Cooperativity

Small changes in ligand concentration make large, non-linear changes in receptor response

amplification

Often due to enzyme cascades

Binding of a single signal molecule may trigger release of 20 response molecules

Each response molecule may bind with 20 other secondary targets

To release 20 x 20 or 400 tertiary response molecules.

And so on and so on...

Desensitization/Adaptation

When signal present continuously, response falls off

Usually due to feedback loop that shuts down system when turned on

After falls below a threshold, response returns

Integration

Multiple signals may be integrated together in final response

Allows for fine tuning

Better homeostasis of organism

Conservation

thousands of different biological signals and responses

10 ? Basic protein components in system

Book Concentrates on 6 major signal transduction systems (based on type of receptor)

12.2 G Protein Coupled receptors

12.3 Receptor Tyrosine Kinases

12.4 Receptor guanylyl cyclases

12.6 Gated Ion channels

12.7 Adhesion receptors

12.8 Nuclear (Steroid) receptors

Several of these proteins were introduced to in last chapter. Here see functional/biological context

Books also looks at how work together as a system, but I doubt we will have time to deal with that high a level. The Premeds/prePharmacy should study the entire chapter, people taking Neuro with Dr. Lamb should look at 12.10 and people working with Dr. Siemens should look at 12.9.

While I will not go over any of these sections, do not be surprised if I have a question on the next test asking you to describe one of these systems

12.1 G protein-coupled receptors (GPCRs) and second messengers

3 essential components of system

Plasma membrane receptor

Typically has 7 trans-membrane helices

A guanosine nucleotide-binding protein

The G-Protein that defines the system

It is this that activates the effector enzyme

Effector enzyme

Also bound to membrane

This is how it works

When signal molecules binds to receptor

Receptor activates the G protein

Protein released a bound GDP

Replaces with GTP

G protein leaves receptor G protein complex

G protein binds to Effector enzyme and alters its activity

Effector produces an intracellular second message

(Level of second message can go up or down)

Human Genome has at least 250 GPCR's

hormones, growth factors and other ligands

Another 500 for olfactory (smell) and gustatory (taste)

Implicated in many common diseases (allergies, depression, blindness, diabetes etc)

Close to ½ of all drugs on market target a GPCR system

Book goes into depth on β -adrenergic receptor that mediates effects of epinephrine and is target of beta blocker drugs. We don't have time to go into but great place for you to dig in for extra points in Dr. Lamb's neuro course or Pre-med background.

12.3 Receptor Tyrosine Kinases (RTKs)

Single membrane bound protein

Binds signal molecule on ligand binding domain

Cytoplasmic domain is a protein kinase that phosphorylates TYR on specific target protein

Examples

insulin receptor

epidermal growth factor receptor

Book now uses Insulin receptor for detailed example

Complicated system

several enzymes and messenger cascade

Again very medically interesting, but don't have time at this level

12.4 Receptor Guanylyl Cyclases

Single membrane bound enzyme

When activated converts GTP to second messenger

guanosine 3',5'-cyclic monophosphate (cGMP)

Structure in 1st column of page 445

(Note this is entirely different than the G protein stuff that used GDP and GTP)

Action of second messenger cGMP often mediated by cGMP-dependent protein kinase (GKP)

When activated by cGMP, GKP phosphorylates Ser and Thr on target proteins

cGMP carries different messages in different tissues

kidney and intestine changes ion transport and water retention

cardiac muscle - triggers relaxation

May be involved in brain function

Guanylyl cyclase is used in cells response to NO (nitric oxide)

This cyclase is involved with how nitroglycerin eases pain of angina

Also involved in how Viagra works

12.5 Multivalent adaptor Proteins and Membrane rafts

In many of the above systems have seen protein kinases that phosphorylate Tyr, Ser and Thr

Reversible phosphorylation makes or destroys docking sites with other proteins

Many of these different proteins from different signal cascades interact together hence the term multi-valent adaptor proteins

Can be in soluble complexes in cytosol for globular proteins

Can be in membrane rafts for membrane bound proteins

Big medical implications on how drugs and diseases all interact

12.6 Gated Ion Channels

Class of cells called 'excitable'

Detect external signal - convert to electrical signal

Electrical signal is a change in membrane potential

Electrical signal then may be passed on to another cell

central role in

nerve conduction

muscle contraction

hormone secretion

sensory processes

learning and memory

Excitability of sensory cells, neurons myocytes - depends on ion channels

Particularly Na^+ K^+ Ca^{2+} and Cl^-

That is why looked at last chapter

These channels are gated

Remain open or closed depending on activation of receptor or membrane potential

Putting pieces together from last chapter

Unstimulated cell

Most animal cells have Na^+ K^+ ATPase

Pumps 3 Na out of cell and 2 K in

So more + of outside less + on inside

Net V_m -50 to -70 mV

(- sign says more negative on inside,

actually here less positive on inside because fewer positives)

Many cells also have Plasma membrane Ca pumps

Pumps Ca out of cell

Or SERCA's

(Sarcoplasmic and Endoplasmic reticulum Ca pumps)

That pump Ca out of cytosol in into endoplasmic reticulum

$[\text{Cl}^-]$ inside > $[\text{Cl}^-]$ outside

Can't find reference to a pump?

May be just because Cl did not get pumped out with Na by Na/K ATPase

Cell with ion channels open

Last chapter saw ion channels - let a specific ion down its [] gradient

Na Channel would let Na into cell would reduce potential

Depolarize

Cl Channel would let Cl out of cell would reduce potential

Depolarize

Ca channel would let Ca into cell and would reduce potential

Depolarize

K Channel would let K out of cell would increase negative potential

Hyperpolarize!

Precisely timed opening and closing of channels results in transient changes in membrane potentials that underlie electrical signaling

Changes in potential and Ca conc causes skeletal muscles to contract

Again will have to skip details

12.7 Integrins

proteins that mediate cell adhesion to each other or to matrix
Also carry information signals

Figure 12-28

Mammalian genome

18 α 's

8 β 's

So far 24 different integrins (Statistically should be $!8 \times 8 = 144!$)

Used in embryonic development blood clotting immune cell function, tumor growth and metastasis

Extracellular ligand include

collagen, Fibrinogen, fibronectin

All have common Arg-Gly-Asp sequence (RGD)

Integrins extend short distance into cytoplasm

On inside of cell interact with cytoskeleton

coordinate cytoskeletal position with extracellular adhesion

Governs shape motility polarity and differentiation of cells

12.8 Steroid effects (figure 12-29)

Will see details in second semester chapter 28 gene regulation

These signals go straight to nucleus to change gene expression.

Steroid hormones (just saw in chapter 10)

Too hydrophobic to dissolve in blood

carried by carrier proteins from origin to target

Don't need membrane transport because diffuse through membrane

(But I've never seen anybody talk about how get through cytoplasm!)

Bind to specific proteins in nucleus

apoproteins (ones without steroid)

often suppress transcription of target genes

Presence of steroid releases suppression

Genes around hormone response element (HRE) get enhances expression

(HRE refers to sequence on DNA that repression protein binds to)

In general these responses are slow (hours to days)

Some steroid responses much faster

Estrogen dilation of blood vessels

must use different mechanism!

Lots of systems in this chapter that integrate different 1st semester subjects together.
Rich place to find questions for a final!