Drugs_Receptor Interactions And Pharmacodynamics

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Pharmacodynamics:هي تاثير الدواء على الجسم
والconcentration مال ال drug ياثر على مدى الاستجابة لهذا ال drug واححنا نعرف ال responseاما يكون beneficial or harmful.

عن طريق ارتباط ال drug و الreceptor.

_ مكان الreceptorاما على سطح الخلية او داخل الخلية.

_ receptorهو عبارة عن اي biological moleculesbiological moleculesترتبط وية الدرك وتسوي رسبونس مثل البروتينات الاحماض الامينية وحتى الانزيمات تشتغل كرسبترات للدرك.

_اكو مصطلحDrugs act as signals, and **signal transduction** their receptors act as signal detectors. Receptors transduce their recognition of a bound agonist by initiating a series of

reactions that ultimately result in a specific intracellular response.

(agonistمعناهاالdrugترتبط بreceptorوتسويلة activation

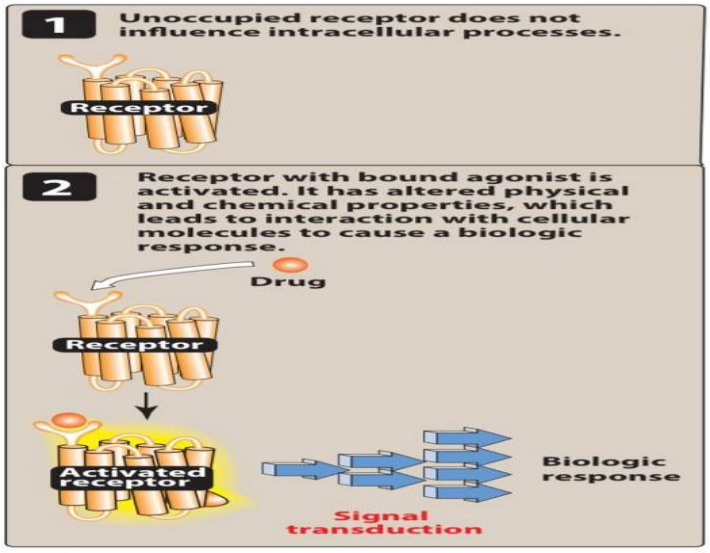


Figure 2.1
The recognition of a drug by a receptor triggers a biologic response.

A. The drug–receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response

مثل عدنا بال cardic cell membraneالبيتا رسبتر فتكون سبيسفك للepinephrine and norepinephrine

وتحتوي على muscarinic receptor تكون سبسفك لل acetylcholine(يعني ال drug من ترتبط ب receptor ويصير response راح يشتغل على acetylcholine)

_فائدة هاي الرسبترات تسير dynamically على الheart function

_اسم الرسبتر حسب type of agonist that interacts best with it.مثل عندي الرسبترات مال الهستامين اسميهن histamine receptor

B. Receptor states

يعني ممكن الرسبتر يكون active وممكن يكون inactive.

C. Major receptor families

انواع الرسبترات راح اوضحها بالرسم:

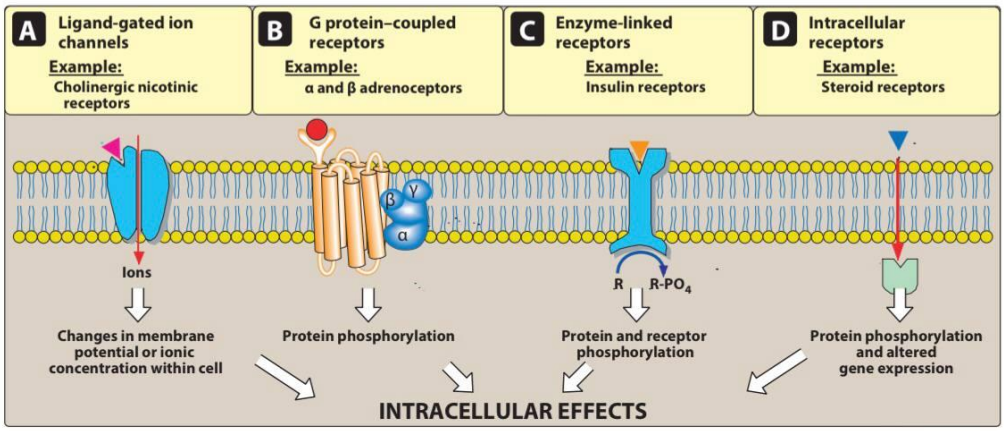


Figure 2.2
Transmembrane signaling mechanisms. **A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. **D.** Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

_1Transmembrane ligand-gated ion channels:

a) The extracellular portion of ligand-gated ion channels usually contains the -ligand

binding site.

الفائدة من هذا البايندكThis site the pore through which regulates the shape of

ions can flow across cell membranes.

_2هذا ال channelيبقى مغلق الى ان يجي فد drug agonistيرتبط بالرسبتر يالة يصيرلة open

-3اعتمادا على ionخلال هذا ال channel الرسبترات هذه تادي وظائف مختلفة:

1_NEUROTRANSMISSION

2_CARDIAC OR MUSCULE CONTRACTION

مثال/Acetylcholine ➡binding in nicotinc receptor➡ stimulation receptor➡ results in sodium influx and potassium

outflux, ➡generating an action potential in a neuron or contraction

in skeletal muscle

NOTEagonist stimulation of the

γ-aminobutyric acid (GABA) receptor➡ increases chloride influx

and hyperpolarization of neurons. Voltage-gated ion channels

may also possess ligand-binding sites that can regulate channel

function. For example, local anesthetics bind to the voltage-gated

sodium channel, ➡inhibiting sodium influx ➡decreasing neuronal

conduction

2_Transmembrane G protein–coupled receptors:

1_The extracellular domain of this receptor contains the ligand-binding area, and

the intracellular domain interacts (when activated) with -a G pro

tein or effector molecule.

2_ There are many kinds of G proteins (for

example, Gs, Gi, and Gq), but they all are composed of three pro

tein subunits.

,a) The α subunit binds guanosine triphosphate (GTP

b) the β and

-c) γ subunits anchor the G protein in the cell mem

brane .

3_ Binding of an agonist to the receptor increases

GTP binding to the α subunit, causing dissociation of the α-GTP

complex from the β,γ complex. These two complexes can then

interact with other cellular effectors, usually an enzyme, ,a protein

or an ion channel, that are responsible for further actions within

the cell. These responses usually last several seconds to .minutes

Sometimes, the activated effectors produce second messengers

that further activate other effectors in the cell, causing a signal

cascade effect.

noteA common effector, activated by Gs and inhibited by Gi, is adenylyl

cyclase, which produces the second messenger cyclic adenosine

monophosphate (cAMP). Gq activates phospholipase C, -gener

ating two other second messengers: inositol 1,4,5-trisphosphate

IP3) and diacylglycerol (DAG). DAG and cAMP activate) different

protein kinases within the cell, leading to a myriad of physiological

effects. IP3 regulates intracellular free calcium concentrations, as

.well as some protein kinases

3_Enzyme-linked receptors:

1_ These receptors consists of

a protein that may form dimers or multisubunit .complexes

2_ When

activated, these receptors undergo conformational changes

resulting in increased cytosolic enzyme activity, depending their structure and function

2_This response lasts

on the order of minutes to hours

-3_The most common enzyme

linked receptors (epidermal growth factor, platelet-derived

growth factor, atrial natriuretic peptide, insulin, and -others) pos

sess tyrosine kinase activity as part of their structure.

The

activated receptor phosphorylates tyrosine

residues on itself and

then other specific proteins .Phosphorylation ➡modify the structure of the target protein➡

acting as a molecular switch. For example, when the peptide

hormone (insulin)binds to two of its receptor subunits, ➡their

intrinsic tyrosine kinase activity causes autophosphorylation ➡

the receptor itself. In turn, the phosphorylated receptor -phos

phorylates other peptides or proteins that subsequently activate

other important cellular signals. This cascade of activations

results in a multiplication of the initial signal, much like that with

.G protein–coupled receptors

4_ :Intracellular receptors

1_the ligand must diffuse into

.the cell to interact with the receptor

In order to

move across the target cell membrane, the ligand must have

sufficient lipid solubility.

– The primary targets of these ligand

receptor complexes are transcription factors in the cell nucleus.

Binding of the ligand with its receptor generally activates the

receptor via dissociation from a variety of binding proteins.

The activated ligand–receptor complex then translocates to the

nucleus, where it often dimerizes before binding to transcription

factors that regulate gene expression. The activation or -inactiva

tion of these factors causes the transcription of DNA into RNA

and translation of RNA into an array of proteins. The time course

of activation and response of these receptors is on the order

of hours to days. For example, steroid hormones exert their

action on target cells via intracellular receptors. Other targets

of intracellular ligands are structural proteins, enzymes, ,RNA

and ribosomes. For example, tubulin is the target of -antineo

plastic agents such as paclitaxel (see Chapter 46), the enzyme

dihydrofolate reductase is the target of antimicrobials such as

trimethoprim.

, and the 50S subunit of the

bacterial ribosome is the target of macrolide antibiotics such as

erythromycin.

Dose response relationships:

a) A. Graded dose–response relations

As the concentration of a drug increases, its pharmacologic effect also

gradually increases until all the receptors are occupied (the maximum

.(effect

_**Potency:** Potency is a measure of the amount of drug necessery

to produce an effect of a given magnitude. he concentration

of drug producing 50% of the maximum effect (EC50) is

usually used to determine potency.

_حتى نفتهم البوتنسي ناخذ مثال/candesartan and

irbesartan are____ angiotensin receptor blockers that are used to

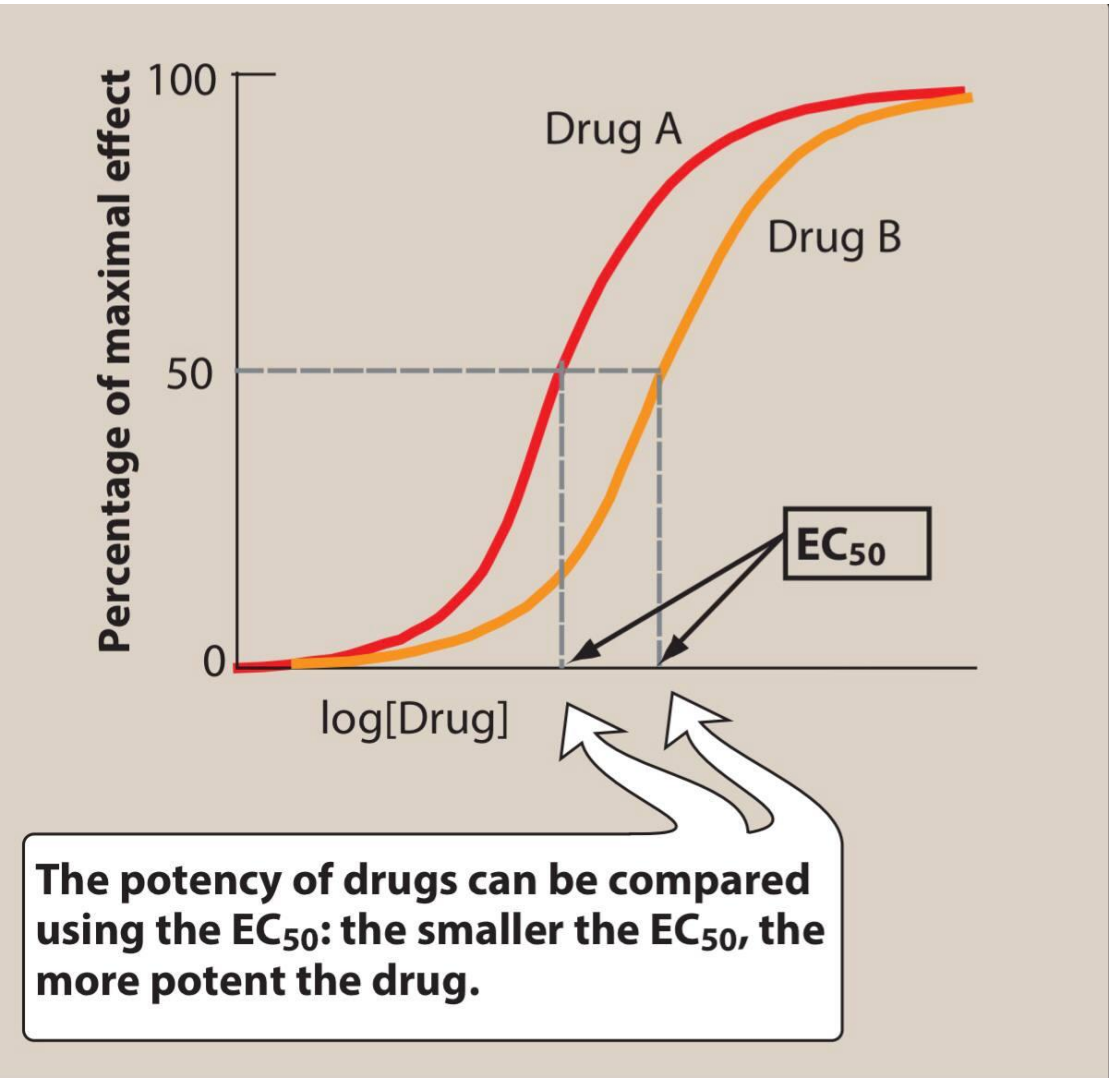
treat hypertension

The therapeutic dose range for candesartan

is 4 to 32 mg, as compared to 75 to 300 mg for irbesartan.

Therefore, candesartan is more potent than is irbesartan (it has a lower EC50 value,

يعني استنتج ان ال drugاللي باقل دوز ينطي therapeutic effectهو اللي يكون more potentكما موضح بالرسم



اعتبر:

A___CANDESARTAN,B__IRBESARTAN

_Efficacy is the magnitude of response a drug causes when

it interacts with a receptor. Efficacy is dependent on the number of

drug–receptor complexes formed and the intrinsic activity of the drug

its ability to activate the receptor and cause a cellular) .(response

Maximal efficacy of a drug (Emax) assumes that all receptors are

occupied by the drug, and no increase in response is observed if

a higher concentration of drug is obtained.

,_____ the maximal

response differs between full and partial agonists, even when 100%

of the receptors are occupied by the drug. Similarly, even though an

antagonist occupies 100% of the receptor sites, no receptor activation

results and Emax is zero.

NOTE) __ a drug with greater efficacy is more therapeutically beneficial than is one that is more potent.

B. Effect of drug concentration on receptor binding

The quantitative relationship between drug -concentration and recep

tor occupancy applies the law of mass action to the kinetics of the

:binding of drug and receptor molecules

Drug + → Receptor Drug–receptor complex Biologiceffect.

C. Relationship of drug binding to pharmacologic effect

1) The magnitude

of the response is proportional to the amount of receptors bound or

occupied, 2) the Emax occurs when all receptors are -bound, and 3) bind

ing of the drug to the receptor exhibits no cooperativity

مصطلحات جدا مهمة:

FULL AGONIST	PARTIAL AGONIST	INVERSE AGONIST

1_A. Full agonists If a drug binds to a receptor ➡ produces a maximal biologic response that mimics the response to the endogenous .ligand receptor, ➡ stabilizing the in its active state .and are said to .	partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist have ➡ .than one	RCeptors show a spontaneous conversion from R to R*(INACTIVE RECEPTOR) in the absence of an agonist. Inverse agonists, unlike full agonists, -stabilize the inac tive R(ACTIVE RECEPTOR) form and cause R* to convert to R. This decreases the number of activated receptors to below that observed in the absence of drug
2-all full agonist should produce the same Emax	cannot produce . the same Emax as a full agonist	
have an intrinsic 3_ activity of one	intrinsic activities greater than zero but lessTHAN ONE	have an intrinsic activity less than zero
4_example, phenylephrine is	As the number of receptors	

a full agonist at α1-adrenoceptors, because it produces the same Emax as does the endogenous ligand, -norepinephrine. Upon binding to α1-adrenoceptors on vascular ,smooth muscle phenylephrine stabilizes the receptor in its active state. ➡ This leads to the mobilization of intracellular Ca2+, causing interaction of actin ➡ myosin filaments and ➡shortening of the muscle cells. ➡The diameter of the arteriole	occupied by the partial agonist increases, the Emax would decrease until it reached the Emax of the partial agonist. This potential of partial agonists to act as both an agonist and antagonist may be therapeutically utilized. For example, aripiprazole, an -atypical antipsychotic, is a partial agonist at selected dopamine .receptors Dopaminergic pathways that are overactive tend to be inhibited by	

	aripiprazole, whereas pathways that are underactive .are stimulated This might explain the ability of aripiprazole to improve symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse . effects	decreases, ➡ causing an increase in resistance to blood flow through the vessel and➡ an increase in blood .pressure

Antagonists

Antagonists bind to a receptor with high affinity but -possess zero intrin

sic activity

يعني يجي الانتاكونست وفقط يشغل الرسبتر يسويله بلوك عكس الاكونست يسوي اكنفيشن للرسبتر. الانواع :

1)Competitive antagonists: If both the antagonist and the agonist

bind to the same site on the receptor in a reversible manner, they are

said to be “competitive.” The competitive antagonist -prevents an ago

nist from binding to its receptor and maintains the -receptor in its inac

.tive state

(يعني تصير فد منافسة بين AGONISTو ال ANTAGONIST على الارتباط بالرسبتبربشكل REVERSIBLE فبتالي ال ANTAGONIST

فبتالي يسوي انكتفيشن للرسبتر.واكدر اتغلب على هل التاثير عن طريق اضافة MORE AGONISTلان كلنا هو ريفيرزبل.

_REDUCE agonist potency

2_Irreversible antagonists: Irreversible antagonists bind covalently

to the active site of the receptor, thereby reducing the number of

.receptors available to the agonist

(هاي تعتبر NONCOPETITIVEبالتالي من اسمها اررريفيرزبل مراح نكدر نتغلب على هذا التاثير مثل الاكونست

_reduce agonist efficacy

3_Allosteric antagonists: An allosteric antagonist also causes a

downward shift of the Emax, with no change in the EC50 value of

an agonist. This type of antagonist binds to a site (”(“allosteric site

other than the agonist-binding site and prevents the receptor from

being activated by the agonist

4_Functional antagonism: An antagonist may act at a completely

separate receptor, initiating effects that are functionally opposite

.those of the agonist

(يعني هو راح يفص ل الرسبترات , بالتالي ينطي تاثير يعاكس تاثير الاكونست وظيفيا).

Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the -dose that pro

duces toxicity in half the population (TD50) to the dose that produces

a clinically desired or effective response (ED50) in half :the population

/ TI = TD50 ED50

The TI is a measure of a drug’s safety, because a larger -value indi

cates a wide margin between doses that are effective and doses that

are toxic

REF. LIPINCOTT

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