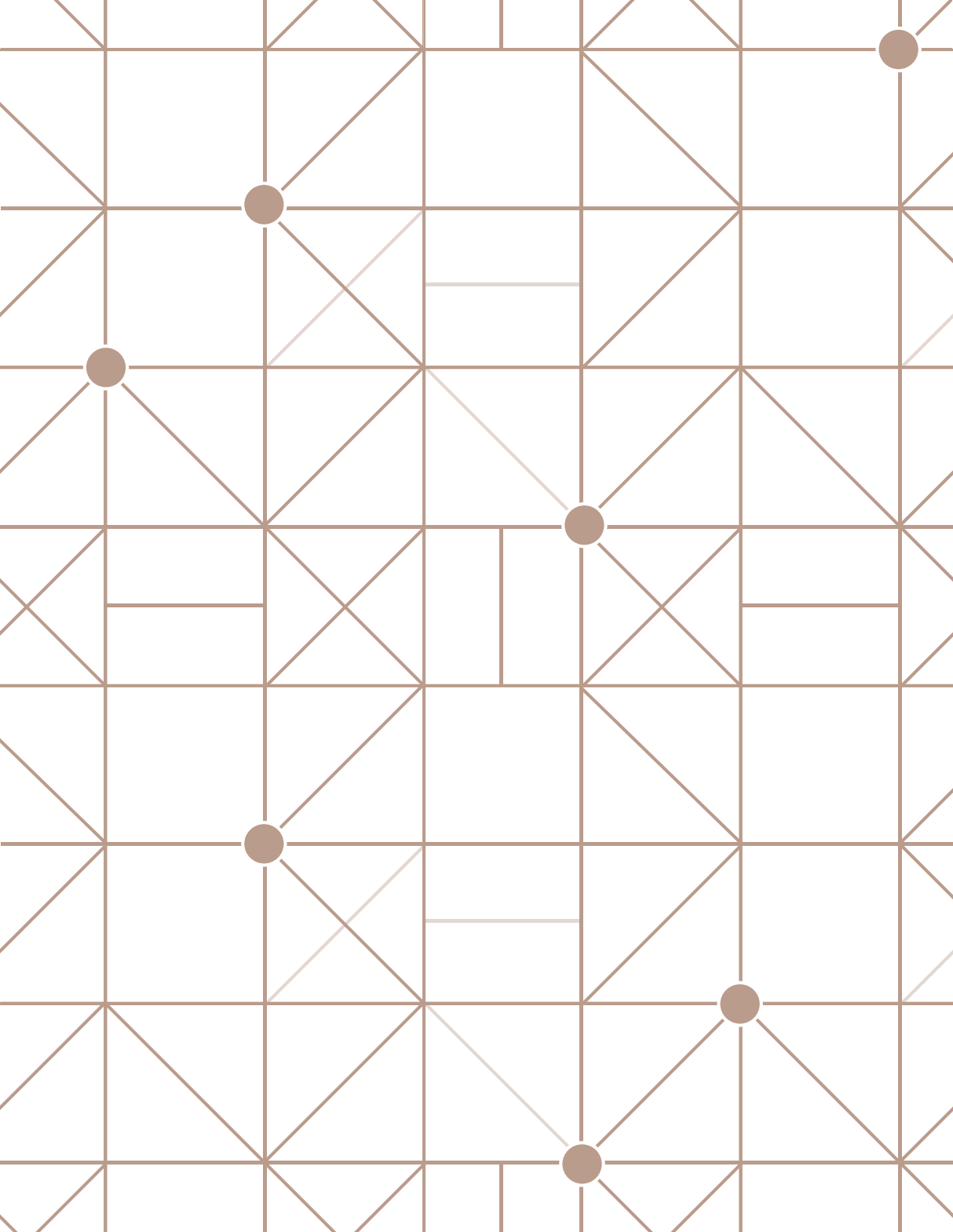


Drug Doses – Clinical Response

- The prescriber → must understand how Drug-receptor interaction
  - ↳ To make rational therapeutic decisions

Underlie :-

- ① Nature + ② Cause of **Variation in pharmacologic responsiveness**
  - Ex → 2 patients → take same dose of drug → 1 patient → response → in 10 min
    2 patient → response → in an ahour
- **Clinical implications** of selectivity of drug action
  - → Higher selectivity → less side effects – good therapeutic
- The relation between **Dose + Response** in patients :- Dose amount → Perfect response

Relations

1 Graded doses (individual)

Response → Graded effect
gradual
Continuous
↓ ex

صوص السكري بيك يكون لا عدة قوادات
و جرعة الدواء مختلفة من شخص لآخر
baseline : 250 g → one dose : 230 g
insuline many doses : 180 g

2 Quantal dose (population)

Response → All-yes – NO
↓ ex
Inffection : pneumonia
Drug : anti-biotic
NO / yes
Healing

Graded - Dose

increase ↑ — increase ↑

○ Magintude of drug response (pharmacologic effect) depends on → Drug concentration (Dose) at receptor site

Determined by :- ① Dose of drug

② factors characteristics of the drug pharmacokinetics profile

↓ rate ↓ of ↓

absorption — distribution — Metabolism

Intestine - stomach - skin | fat - blood - All body

○ Graded dose – Response Carve :- graph

- General shape :- Rectangular hyperbola
- use :- plotting ○ Magintude of response ↑ + ○ Concentration - doses of drug ↑

- It's determined 2 properties :-

(high potency – higher Iffinety - low dose)

	Potency	Efficacy
Deffinition	A measure of : the amount of drug necessary to produce an effect of given magnitude - (necessary magnitude - lower drug amount)	The ability of drug to elicit a response to receptor (no amount neaded)
Effected by	↑○ Receptor concentration - Density ↑○ Efficiency : Stimulation response mechanism ↑○ Affinity : strength of interaction - binding ligand-receptor ↑○ Efficacy Ex→ metabolism spead is varies	↑○ Number of drug-receptor complex ↑○ Efficiency of the coupling receptor activation to cellular response

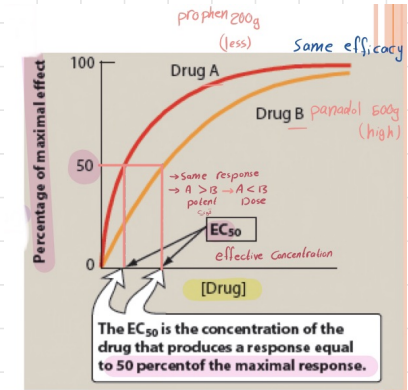
Potency

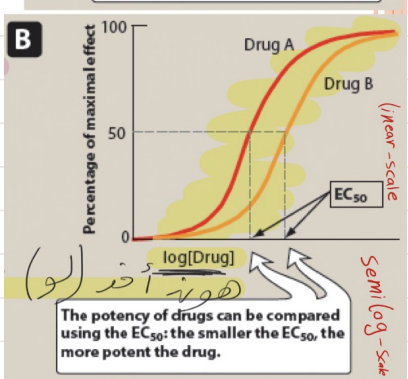
Efficacy

Explain

Concentration of drug produce an effect that is 50 percent of maximum used to determine potency

EC_{50}





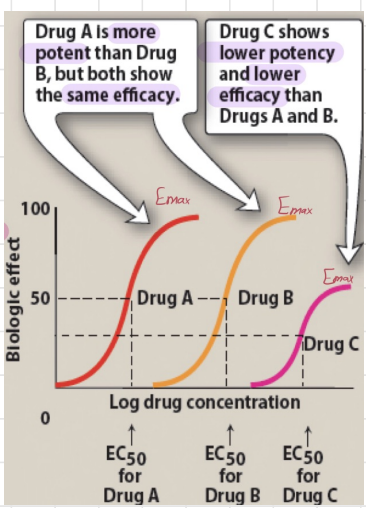
→ Curve shift to lift
→ more potent
→ smaller EC50

- Maximum efficacy :-
  - All receptors are occupied by drugs
  - No increase in response :- if more drugs are added

- The hight of maximal response use to → measure maximal efficacy of agonist drug

Used to Compare efficacy of Similar acting agonists

Example



→ A drug great efficacy → more therapeutically beneficial → than more potent (full agonist)

Drug concentration —on→ Receptor binding

occupancy

- Quantitative relationship

Drug + Receptor ⟷ Drug-receptor Complex → Biologic effect

[free drug] ↑ ∴ Ratio of [Binding receptor to Total receptors]

Approachs Unity

- بشكل أدق: لا نتحدث عن عدد و إنما نسبة Bound → Total receptors

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]}$$

[D] = the concentration of free drug,
[DR] = the concentration of bound drug,
[Rt] = the total concentration of receptors and is equal to the sum of the concentrations of unbound (free)receptors and bound receptors,
Kd = the equilibrium dissociation constant for the drug from the receptor.
ثابت التفاعل

↓ Determine it

- ↑ Kd → ↓ Affinety → ↓ interaction

Types of antagonists

1 Chemical Antagonists :-

Defintion → Compined with agonist + inactivates it way from Receptor - Tissue

Examples →

- Alkaline anti-acids : Nuetralize HCl in stomach of peptic ulcer
- Protamine (base) : Nuetralize anti-coagulent Heparin in plasma
- Chelating agents : Binding with higher affenity heavey metals (lead - mercury - arsenic) in plasma - tissue preventing their tissue toxicity

2 physiological Antagonists :-

Defintion →
- It's agonist in Same tissue
- Act by mechanisms - Receptor different from specific agonist
- Quickly reverse it's action

Examples →

- Adrenaline :
  - IM taking
  - quick acting as antagonist
  - to Histamine → Released from mast cells - basophile
  - In Anaphylactic shock

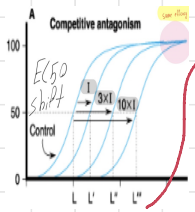
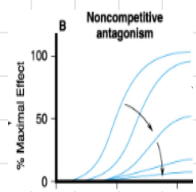
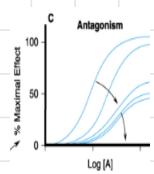
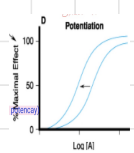
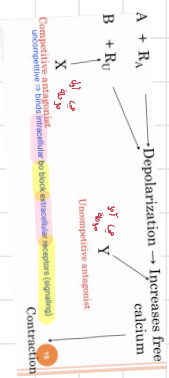
reason: Same receptor - Drug (similarity in chemical structure to agonist)

Different receptor - Endogenous ligand

3 pharmacological antagonist :-

Defintion →
- The Antagonist is high affinity to the receptor
- The Antagonist has No efficacy - intrinsic activity → of drug determine (active: full / partially)
- If their no agonist → The antagonist has no affect
- If their agonist (function) → Decrease the effect of agonist

1) Blocking drug ability to bind to receptor
2) Blocking drug ability to activate receptor

Antagonists	potency	Efficacy	site of receptor	Graph	
Competitive reversible	Decrease increase EC_{50}	Constant	Same site of agonist receptor ↓ because of it's semilarily structure	 Dr curve	○ Ionic bond ○ shift to right ○ The Emax can restord by increase [agonist] ○ ↑ [Antagonist] ↑ shift to right
non-Competilive irreversible	no shift Constant Constant EC_{50}	Decrease	Same site of same agonist receptor	 ↓ [Antagonist] ↓ maximal response	○ Covelent bond ○ strong binding or ○ dissociate very slowely ○ response curve Shift slightly right reason ○ Emax can't restord ↓ remaing availble receptors
non-Competilive Allosteric	Constant — Constant EC_{50}	Decrease	Different site of same receptor		○ Covelent bond
enhacment	Increase — decrease EC_{50}	Constant	Different site of same receptor		○ Covelent bond ○ ↑ bind of agonist with receptor
Uncompetitive	Constant	Decrease	Different receptor		○ Located more distaly in the effector mechanicsm ○ Dose-response Curve = noncompetilive irreversible

Compatilive reversible:

Propranolol (inderal 10,20,40 mlg) مثال الدكتور للفهم،اسم الدواء
e.g: inderal lO mlg half 💊 for stress,Antagonist for adrenaline/ Beta 2 receptor blocker
⇒ in situation makes you feel stressed you get half 💊 to block adrenaline from binding to beta2 receptors ,but if the situation gets more terrible, the secretion of adrenaline will increase ,in turn the concentration o f adrenaline raise above the antagonist ,so you will need higher dose (from graph get higher dose 3×1 times) ,so you will get inderal 20 mlg to decrease your stress and so on
move terrible ⇒inderal 40 mlg (to graph its lOx1 dose)
(compitilive between inderal and adrena line)

➢The affinity of competitive antagonist K_I to its receptors is calculated from :

$$C^*/C = 1 + [I] / K_I$$

where C* is concentration of agonist that restores response in presence of antagonist concentration [I], and C is agonist concentration giving this response in absence of antagonist.

Examples:

- atropine is a competitive reversible antagonist to Ach at muscarinic receptors;
- Beta-blockers are competitive antagonists to adrenaline at beta –adrenergic receptors.

)→ Up-regulation

Non-Compatilive Allosteric Enhancement:

benzodiazepines to GABA-A receptors can enhance the depressant GABA effect on brain neurons.

Receptor regulation

UP- regulation

- ↑ use of Antagonists
- ↑ number - effinity of specific receptors

(supersensitivity)

reason ↓

1) prolonged used of Antagonist
   ↓
   lack binding receptors to agonist for long period
   ↓ Ex
   Using of Atrophine (sympathetic)
   Abolishing (إلغاء) of parasympathetic stimulation

2) Disease :-
   ↓ Ex
   Hyperthyrodism :

1) excess thyriod H
2) proliferation β-adrenergic receptors (in heart)
3) increase risk of Cardiac arrythmia from 1) Adrenaline
   2) β-adrenoceptor ⟲ (agonist)

build new receptor ↑ ↓

Down - regulation

(Tolerance)

- ↑ use of Agonist
- ↓ number - effinity of specific receptor
  (prolonged use of agonist)
  ↓
  Days - weaks

Decrease in respond to agonist

- To restore intensity of response
  ↓
  Increase dose of agonist

Tachyphylaxis

:- Rapidly developing tolerance

- Not due to Down-regulation
- Because of Repeated of use largedoses of direct agonist :-
  - short dose interval
  - Continous IV infusion of agonist

↓ Due to

- Desenization of receptors :

→ Change in receptor

Lead to : phosphorylation of receptor

Result : Diminshes (تقلل) the ability of receptor Bind → to G-protein

- Depletion (نفاذ) of intracellular stores of transmitters :

Ex → Depletion of Noradrenaline in vesicles in sympathatic nerve ends

↓ reason

Repeated use of indrect sympathomimetic amphetamine

- Restore response :-

→ Agonist drug must be stopped for short time to :-

1) Recovery receptors
2) Stores of transmitters

- Different receptor of agonist → physcio

  Same receptor of agonist → pharma.. / chemical

- physio ...gnist → Not a Drug

2. INDIVIDUALS USUALLY SHOW VARIATION IN INTENSITY OF RESPONSE TO DRUGS DUE TO :

1. **Variation in concentration of drug that reaches the tissue receptors :** due to pharmacokinetic factors
2. **Abnormality in receptor number or function :** either genetically-determined or acquired due to up-regulation or down-regulation
3. **Post-receptor defect inside cells** :

   This is an important cause of response variation

4. **Variation in Concentration of an Endogenous Receptor Ligand**

   contributes greatly to variability in responses to pharmacologic antagonists.

1. variation⇒ e.g: عندك واحد ماكل منسف والثاني مش ماكل إشي ،
and both of them got vitamin D , the amount of drug reached the target tissue in first guy is higher than in second guy
Due to the high amount of lipids helped absorption of drug
this called ⇒ gastric reten tion time حنو خده القدام بالتفصيل

3. pos t_ receptor defect⇒ mean that signaling (biological response) may differ from Patiant to another

4. Endogenous receptor ligand⇒ as Ach,which is endogenous substance, may differ in amount between Paiants, So if we give atropine 10mlg ,someone will have Emax while other will have lower due to the low amount of Ach or the endogenous receptor