Pharmacology

→ $V_d = \frac{\text{Amount of Drug in Body}}{C_0}$

→ $t_{1/2} \approx 0.693 \frac{V_d}{CL}$

* $V = \frac{V_{max}[C]}{K_m + [C]}$ ← rate of drug metabolism

● most drugs clinically w/ low conc.

⇒ $V = \frac{V_{max}[C]}{K_m}$ ← $[C] \ll K_m$ / first order kinetics.

● drugs w/ high conc.

⇒ $V = V_{max}$ ← $[C] \gg K_m$ / zero order kinetics
e.g Aspirin
Ethanol
phenytoin.

$V = \frac{V_{max}[C]}{[C]}$

* $C_{ss} = \frac{\text{Infusion Rate}}{Cl}$

* faster infusion Rate → same time to Achieve Css
↳ Css is More

*rate constant to Achieve Css = Rate constant of TBE
$= t_{1/2}$

rate Not affected by infusion rate Nor frequency.

* Dosing Rate = $\frac{(\text{Target } C_p)(CL)}{F}$ ← BioAvailability.

* Loading Dose = $\frac{V_d * \text{desired } C_{ss}}{F}$ ← when IV ⇒ F=1

* Additional Dosage Needed = $V_d (C_2 - C_1)$

$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]}$ && $\frac{[E]}{[E_{max}]} = \frac{[D]}{K_d + [D]}$

Clinical Trials

مؤسسة فاي للعلوم
Phi Science Institute

phase 0
- ✓ 10–15
- ✓ first-in-human
- ✓ Human-Microdosing studies.
- ✓ speed up development of drug.
- ✓ subtherapeutic pharmacokinetics & pharmacodynamics

phase 1
- ✓ dosage ~~effect~~ / safety
- ✓ 25–30 ppl
- ✓ find Maximum tolerated dose.
- ✓ Healthy volunteers
- ✓ Non blind.
- ✓ safety / pharmaco-kinetics.
- ✓ Research centres by trained clinical pharmacologists.

phase 2
- ✓ efficacy
- ✓ 100–200
- ✓ detect broad range of toxicity.
- ✓ sick/patients.
- ✓ single-blind
- ✓ special clinical centres (university hospitals.

phase 3
- ✓ safety & efficacy.
- ✓ thousands
- ✓ minimise errors by placebo.
- ✓ patients.
- ✓ double-blind & crossover.
- ✓ disease specialists.
- ✓ NDA takes up to 3 yrs.

phase IV
- ✓ safety in large # of ppl
- ✓ No duration
- ✓ rare toxicity.

High MW
too large
extensively plasma bound ⇒ Plasma

Low MW
hydrophilic ⇒ ECF.

Low MW
lipophilic ⇒ TBW

Vd ⇒ Calculate loading dose.

$$= \frac{dose}{Co}$$

depends on blood flow (lipophilic).

Drug Metabolism

Lipophilic drugs → Metabolism → Hydrophilic → Excretion.

↓x

~~Or~~ reabsorbed by distal tubule

* → phase 1 (ox., red., Hydrolysis) → changed: Activated; inactivated; unchanged → phase 2 → Conjugation products (inactive / Hydrophilic).

* Phase 1:

-OH or -NH2

NO P450 sys.

P450 sys.

* Cytochrome P450 isozymes
(Microsomal Mixed function oxidases)
⇒ Heme-containing; all cells (esp. GI & liver)

* imp:
→ Metabolism of Endogenous.
→ Biotransformation of Exogenous.

* CYP3A4 (1. 2. 3. 4.) ⇒ 1. superfamily
2. family
3. subfamily
4. isozyme.

* Major 4
CYP3A4/5 —
CYP 2D6 → Codiene
CYP 2C8/9
CYP 1A2
} polymorphism.
see CYP2C19 → Clopidogrel.

* Induced By:
Xenobiotics.
- phenobarbital
- rifampin
- carbamazepine

↑ drug Metabolism
⇓
↑[D] in plasma
↑Activity if Active Metabolite
↓Activity if Inactive Metabolite.
↓Therapeutic Effect.

* Inhibited By: OP EM KC RN
- Omeprazole (↑warfarin)
- erythromycin
- ketoconazole
- Ritonavir
- Grapefruit Juice (inhibits CYP3A4)

⇓
↑conc. of NO SIM CM
Nifedipine, Clarithromycin, Simvastatin.

① Amine Oxidation
→ Catecholamines / Histamine
② Alcohol Dehydrogenation.
→ Ethanol Oxidation.
③ Esterases
→ Aspirin in liver
④ Hydrolysis
→ Procaine

← TBC →

* Phase II :

~~GAS~~ SAGA

Conjugation w/ Glucuronic Acid, Sulfuric Acid, Acetic Acid, or Amino Acid.

⇒ More Hydrophilic Polarity

Except Morphine-6-Glucuronide ⇒ More potent than Morphine.

* Glucuronidation ⇒ Most common/potent.

Pharmacodynamics II

Dose-Response Curve ⇒ Rectangular Hyperbola

↳ potency & efficacy → Emax
- depends on:
  1. # of ligand-Receptor complexes
  2. intrinsic Activity of Drug.
- ↓Anagonist Emax = 0.

↓

EC50

↓

Angiotensin Receptor Blockers // Treat Hypertension

e.g. Candesartan — Therap. dose Range → 4-32 mg.

vs. Arbesartan → 75-300mg.

$* \frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]}$ ⇒ @ Dose-Response curve if: ① Response Magnitude proportional to # bound Receptors
② Emax = all Receptors bound
③ No cooperativity.

↑ determines Affinity. (↑Kd, ↓Affinity).

$* \frac{[E]}{[Emax]} = \frac{[D]}{K_d + [D]}$

↑ effect.

(Based on Intrinsic Activity & Emax)

Drugs

Full Agonist
Intrinsic Activity = 1 (Ai)

e.g. Phenylephrine (Epinephrine).
@ α1
→ vasoconstriction.
↑BP.

partial Agonist
0 < Ai < 1

* Antagonist to full Agonist.

e.g. Aripiprazole
@ Dopamine Receptors.
(Atypical Antipsychotic)
(↓ Schizophrenia)).

Inverse Agonist
Ai < 0

Antagonist
Ai = 0

Competitive
e.g. Terazosin (w/ competitive NE @ α1)
↓BP
* shift Agonists' Dose-Response curve to the right.
* ↑EC50 of Agonist
* same Emax.

Non-competitive

Irreversible
* covalent
* same EC50 of Agonist
* ↓Emax.
(active site)

Allosteric
* ↓Emax
* same EC50.
e.g. picrotoxin
@ GABA-Cl⁻ channel.
(inside channel)

functional
* opposite Agonist effect.
e.g. Epinephrine vs Histamine.
* Aka, Physiologic Antagonism

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* Quantal Dose-Response Relationship ≡ population based.
  ≠ effect either occurs or Not.
* ED50 = [drug] causes Response in ½ population
  TD50 = [drug] ≠ Toxicity " " " .

$TI = \frac{TD_{50}}{ED_{50}}$ ↳ drug trials, clinical experience.

↑TI, ↑ safety

e.g. Warfarin (low TI)
Penicillin (high TI)

Drug Receptors

Ligand-Gated ion-channels

→ Nicotinic Cholinergic

→ few Milliseconds

① Nicotinic Receptors + ACh

⇒ Na^+ influx
K^+ outflux

Action potential in Neuron
SKM contraction.

② GABA receptor + Agonist

⇒ Cl^- influx

Hyperpolarisation of Neuron

③ Local Anaesthetic + Voltage-gated ion-channel

⇒ inhibit Na^+ influx

Decrease Neuronal conductance

GPCR

→ G_i, G_s, G_q

→ α, β, γ (e GTP)

→ seconds to minutes.

* G_s, G_i

→ Adenylyl Cyclase & cAMP...

* G_q

⇒ PLC & IP3 + DAG ...

* DAG & cAMP → protein kinases

* IP3 → Ca^{2+} channels & some PK.

* β-Adreno receptors in ♡

⇒ 5-10% spare

Enzyme-linked Receptors

eg.

→ Insulin Receptors.

→ Activation → dimer or Multisubunit Complexes.

→ Minutes to hours.

→ e.g PDGF, EGF, Insulin, ANP

Tyrosine Kinase Activity.

* Insulin Receptors

⇒ 99% spare.

Intracellular Receptors

→ primary target: Transcription factors in Nucleus.

→ dimerises before binding TF

→ hours to days.

→ other targets of IC ligands: enzymes, structural proteins, RNA, Ribosomes.

* e.g. Targets:

① Tubulin
→ Antineoplastic Agents
e.g. Paclitaxel.

② Dihydrofolate Reductase
→ Antimicrobials
e.g. trimethoprim.

③ 50S subunit of Bacterial Ribosom
→ Macrolide Antibiotics
e.g. Erythromycin.

} Tachyphylaxis = Desensitisation.

Cholinergic Receptors

Muscarinic

* GPCR
- M1 → Gastric Parietal cells
- M2 → cardiac cells & SM.
- M3 → Bladder, exocrine glands, & SM

* in Addition to Neuron.

* M_1 or M_3
  ↓
  G_q
  ↓
  PLC
  ↓
  IP_3 & DAG
  ↓ ↓
  Ca^{2+} PKC

* M_2
  ↓
  G_i
  ↓
  inhibit Adenylyl cyclase
  ↓
  ↑ K+ conductance
  (↓ heart rate
  ↓ contraction)

* M1 → Alzheimer's
  M3 → COPD.

Nicotinic.

* 5 subunits.
* ligand-gated ion channels.
* 2 ACh
* Nicotine → @ high conc: blocks
  @ low conc: stimulates.

* in CNS,
  Adrenal Medulla,
  Ganglia, NMJ.
  NM NN

* Ganglia ⇒ selectively Blocked By Mecamylamine

NMJ ⇒ = = = Atracurium

Adrenoreceptors.

1) α → Epinephrine ≥ Norepinephrine >> Isoproterenol.

- α_1 → phenylephrine // SM constriction // GPCR → Gprotein → PLC → IP3 & DAG → @postsynaptic effector organs.
  - α_1 A, B, C, D.
- α_2 → Clonidine // feedback inhibition (Norepinephrine reacts w/ α_2)
  - (inhibitory autoreceptors) → inhibit Norepinephrine
  - (inhibitory heteroreceptors) → inhibit ACh.
  - @presynaptic sympathetic Nerve.
  - @presynaptic parasympathetic.
  - α_2 A, B, C
  - ↓ Adenylyl Cyclase → ↓ [cAMP] ...

α_{1A} Receptors → found on urinary tract & prostate gland // Tamsulosin: to treat Benign Prostatic Hyperplasia.

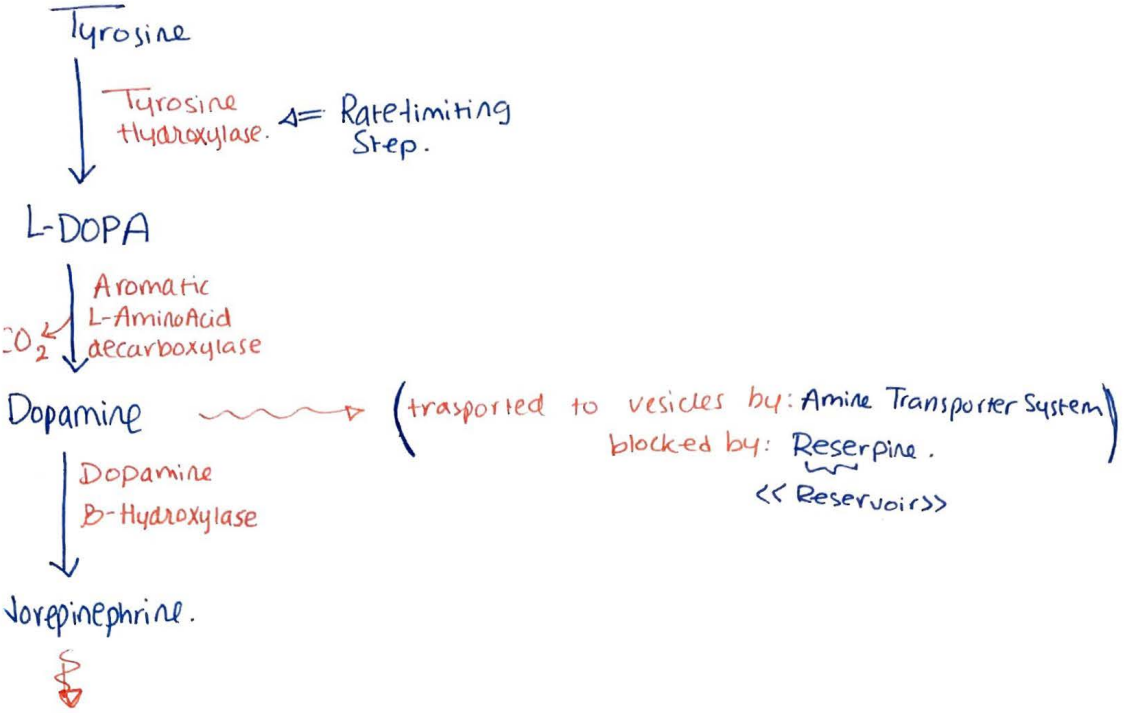
α_{1B} // → blood vessels

2) β → isoproterenol >> epinephrine > Norepinephrine.

- β_1 epinephrine = Norepinephrine → eg. Heart.
- β_2 epinephrine > Norepinephrine eg. vasculature of SkM. (also α_1 but less)
- β_3 lipolysis // Detrusor muscle of bladder.

→ Adenylyl cyclase↑ → [cAMP]↑

Norepinephrine Synthesis



Released @ Synaptic Gap (Blocked by: Guanethidine)

+ use BOTH cAMP & IP_3 lifestyles.

- Reuptake involves Na^+/Cl^--dependent NET

  inhibited By:

  - Tricyclic Antidepressants e.g. imipramine.
  - Serotonin-Norepinephrine Reuptake inhibitors e.g. duloxetine.
  - cocaine.

COMT → in synaptic space (Methylation)

MAO → in Mitochondria - (oxidation.