Veterinary Bioscience: Cells to Systems

VETS30029 / VETS90121

Introduction to Pharmacology: Pharmacodynamics and principles of drug action

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Pharmacology

The study of the effects of ***drugs*** on living things

Veterinary Medicine

- Responsibility and privilege of prescribing ***drugs***
  - as life-saving agents to treat medical conditions
    - acute use for short-term conditions
    - life-long use for chronic conditions
  - to enable surgical procedures
    - regulate consciousness
    - control post-operative pain

Recognise the importance of *safe & effective use of drugs*

Apply in relation to peripheral nervous system and autacoid signalling

Drugs are chemicals that affect physiological function in a specific way

Made by the body

Adrenaline: Increases heart rate
Dilates airways
Can initiate dysrhythmia

Adrenal gland

Made by chemists

Salbutamol: Dilates airways
May increase heart rate

Synthetic molecule

Made by plants

Atropine: Dilated pupils attractive
Dry mouth, photophobia, hallucinations, death!

Atropa Belladonna
Deadly Nightshade

All drugs have more than one action

Safe and effective drug use

Lessons from history

- Drugs can provide relief

  (Hippocrates, 5thC ,B.C.E.)

- All drugs are poisons, dose determines effect

  (Paracelsus, 1493-1541)

- Drugs must bind a molecular target

  (Paul Ehrlich, 1913)

- To get relief you must take some risk

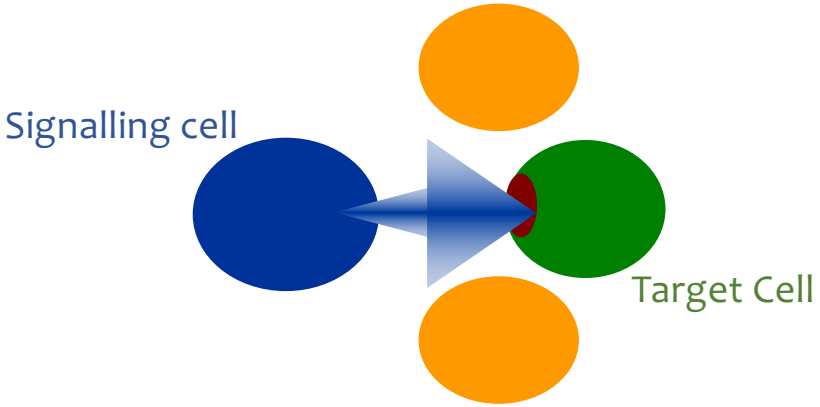
  (Laurence &Black, 1980)

Requires understanding of pharmacological principles

Chemical signalling in the body

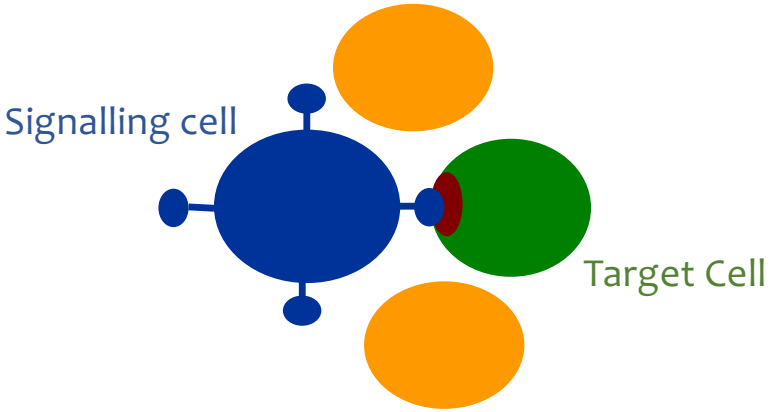
Cells can communicate by:

1. release of molecules



Neurotransmitters (wired networks)
Hormones (broadcast)
Local mediators (shouting)

2. membrane bound molecules

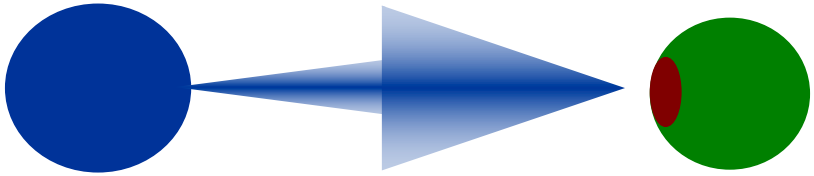


Immune system
(Cellular contact)

Multiple sites of drug action

Molecular targets that drugs can bind

Molecules involved in mediating physiological effects
Receptors, **I**on channels, **C**arriers, **E**nzymes



Transmission + reception = response.

Signalling cell

- Specific Enzymes, Carriers, Ion channels will be involved in synthesis, storage and, possibly, inactivation process
  - **Regulate the concentration**

Target cell

- Specific Receptors recognise the signalling molecule
- transduction / amplification of signal by Enzymes, Carriers & Ion channels
  - **Regulate the response**

Challenge is to recognise targets with therapeutic potential

How drugs work

Health

Neurotransmitters
Hormones
Cytokines

Receptor
Ion Channel
Carrier
Enzyme

Molecular target

Normal function

Disease

Pathological process

Molecular target

Abnormal function

Increased / decreased activity

Disease Treatment

Pathological process

Drug

Molecular target

Restore function

Unwanted actions

Adapted from S Maxwell IUPHAR

At the end of this lecture, you should be able to:

- **Describe how drugs can influence the function of cell, tissues and organs (Pharmacodynamics)**
- Describe the importance of the concentration-response curve in characterising the action of drugs
- Describe processes by which the body may influence the actions of a drug (Pharmacokinetics)

Multiple levels of drug action

Integrated sentient beings!

WHOLE BODY Homeostasis Nerves/hormones
SYSTEMS Cardiovascular/ Renal /CNS
TISSUES Blood vessel/heart
CELLS Single/culture
MEMBRANES
MOLECULES Specific targets
GENES

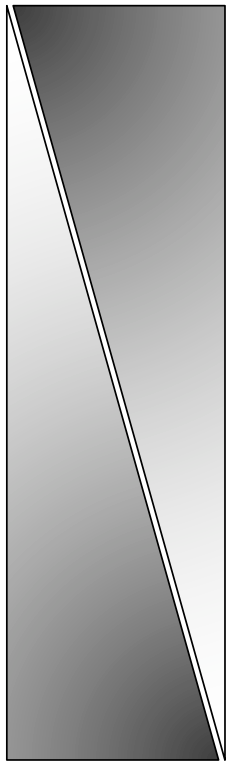
Dose

Concentration

- **R**eceptors
- **I**on channels
- **C**arriers
- **E**nzymes

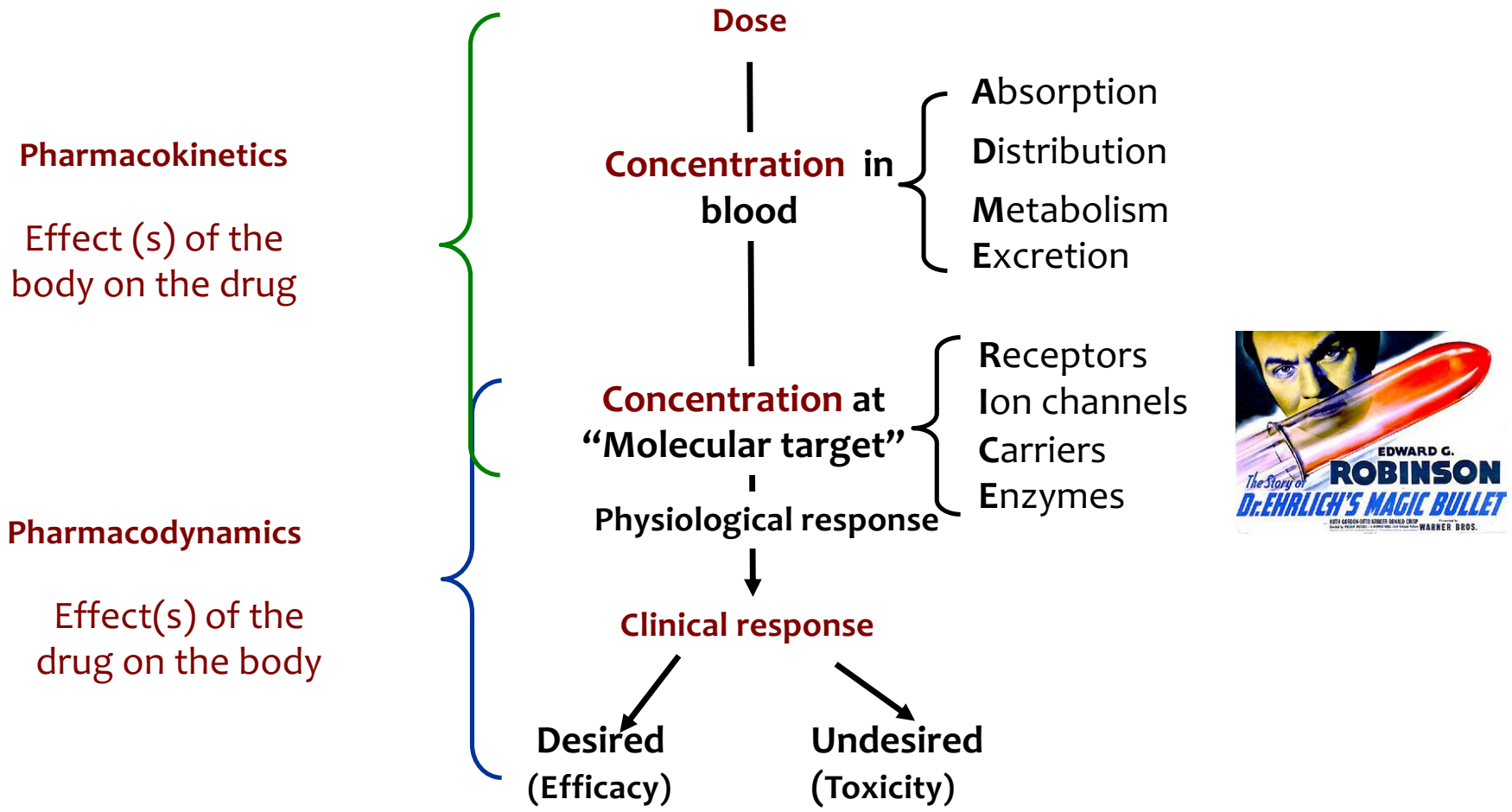
- Nucleic acids

Relevance



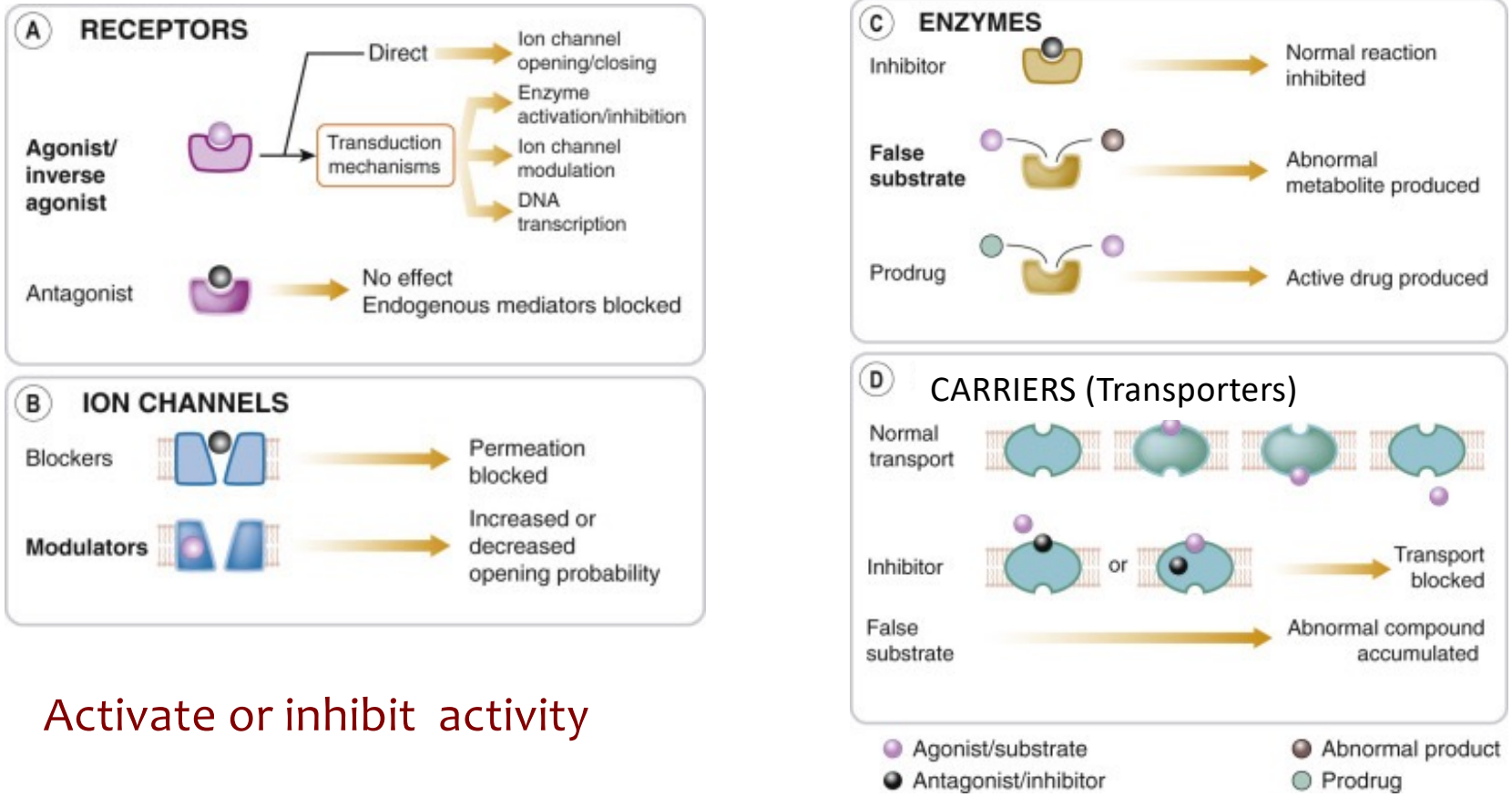
Predictable

All drugs are poisons, dose determines effect



Pharmacology quantifies drug action

Drug interactions with molecular targets



Activate or inhibit activity

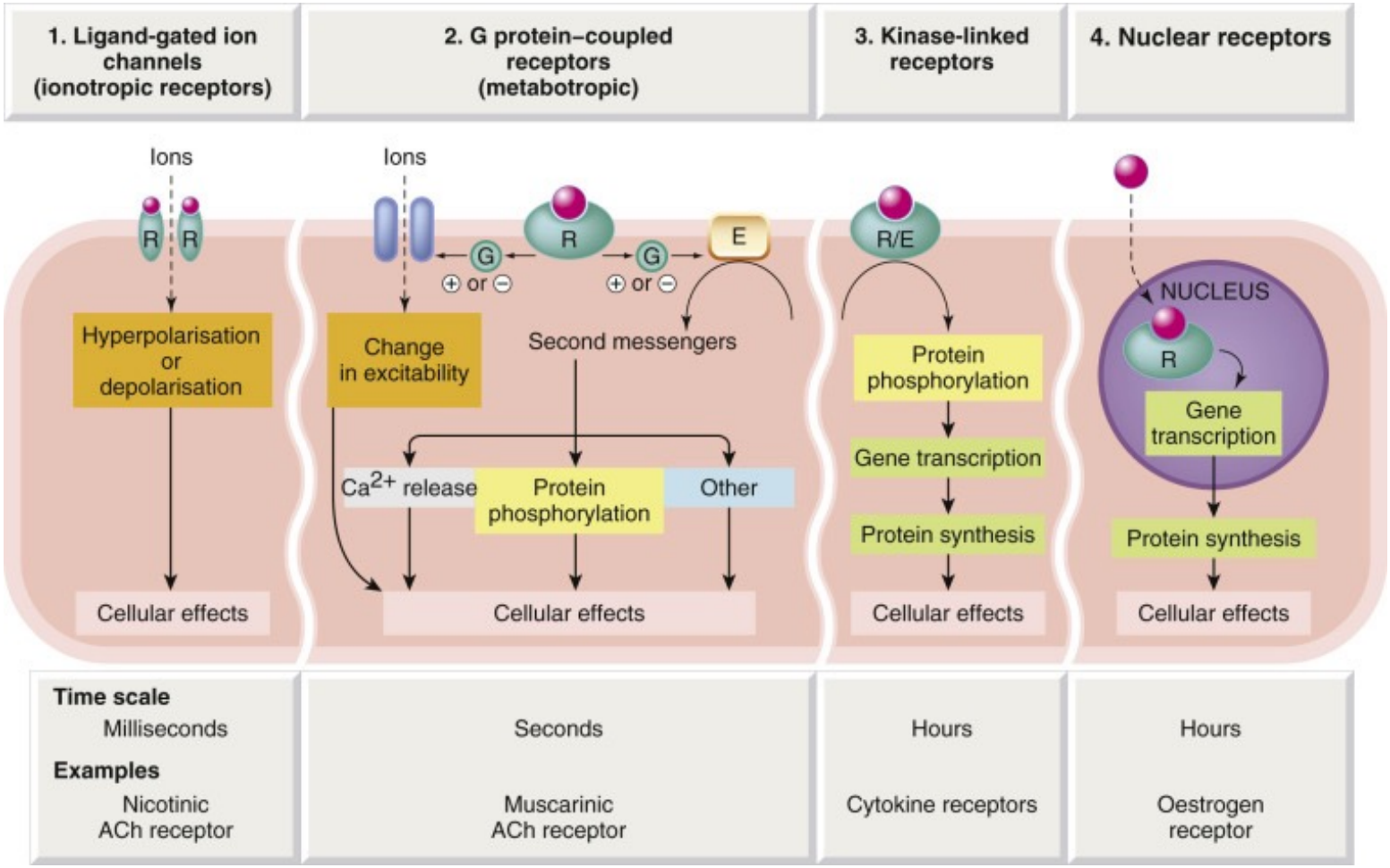
Rang & Dale, 8th Ed Figure 3.1 (Adapted)

Focus on receptors

Receptors

- initiate cellular signalling by chemical mediators
- make drugs powerful & potent
  - amplification through 2nd messengers
  - signalling may involve ion channels, enzymes, carriers
- contribute to specific responses based on drug selectivity
- targetted by 40-60% of therapeutic drugs
- principles applicable to other targets
  - ion channels, enzymes, carriers

Receptor localization and cellular signalling



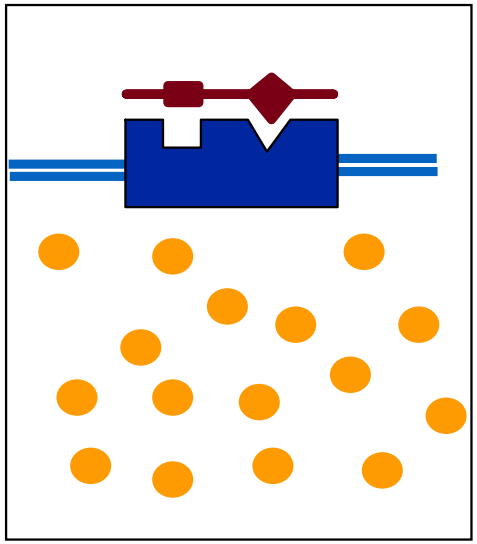
Drug selectivity for acetylcholine receptor subtypes?

Rang& Dale, 8th Ed Figure 3.2

Pharmacodynamics: Drug action

Agonists

Bind and
activate the receptor



Measurable
properties

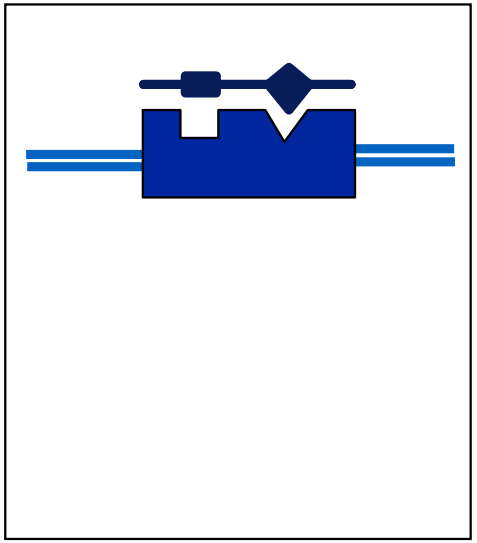
Affinity

Potency

Efficacy

Antagonists

Bind and DO NOT
activate the receptor



Affinity

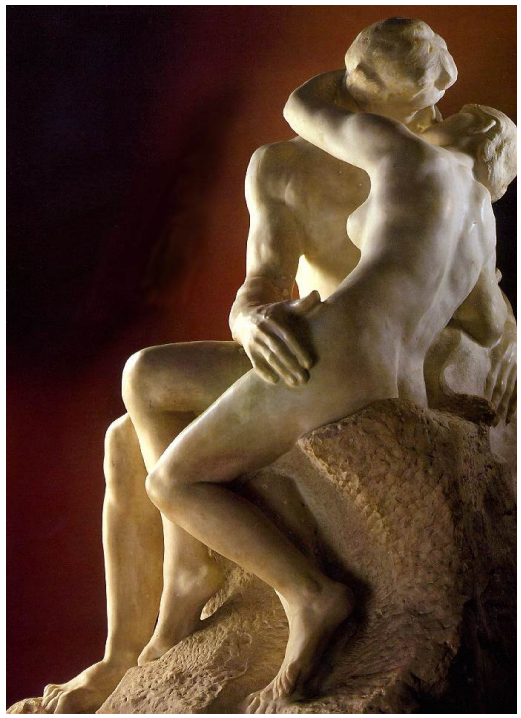
- A quantifiable measure of the molecular attraction of a drug (agonist or antagonist) to the receptor
  - Law of mass action

$$[D]+[R] \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} [DR]$$

D = Drug, R = Receptor

  - Dissociation constant K_D
    - Concentration at which 50% receptors are bound
    - Low K_D means high affinity

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

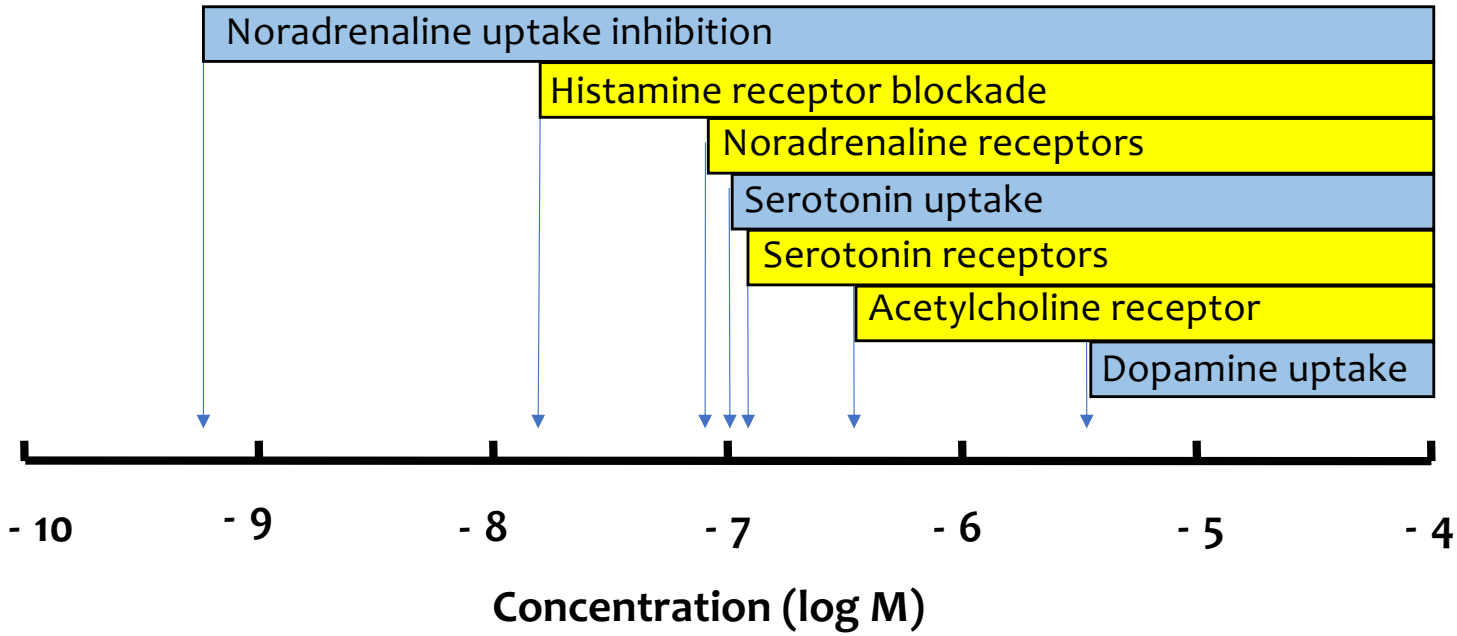


- Drugs can have affinity for different receptors
  - Constant for a given drug-receptor pair
  - Relative affinity gives an indication of the selectivity of a drug

Desipramine - a selective drug?

Desipramine considered a selective noradrenaline uptake inhibitor

- also binds and blocks other targets with lower affinity
  - > 30 fold increase in concentration required



Dose (concentration) determines effect

Adapted from data Bolden-Watson C, Richelson E, 1993, Cusack B, et al. 1994

At the end of this lecture, you should be able to:

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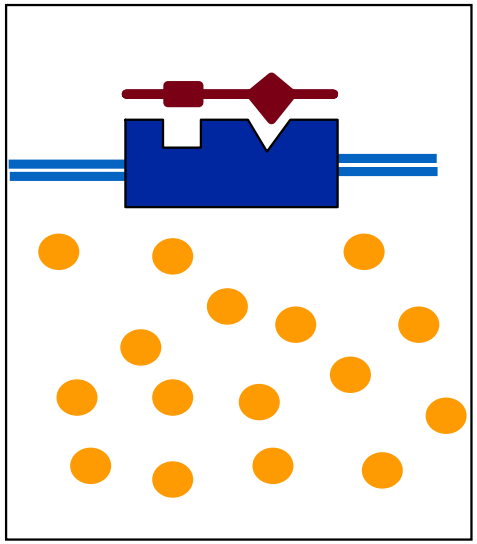
- **Describe the importance of the concentration-response curve in characterising the action of drugs**
- Describe processes by which the body may influence the actions of a drug (Pharmacokinetics)

Drug action at receptors

Agonists

Bind and
activate the receptor



Measurable
property

Affinity

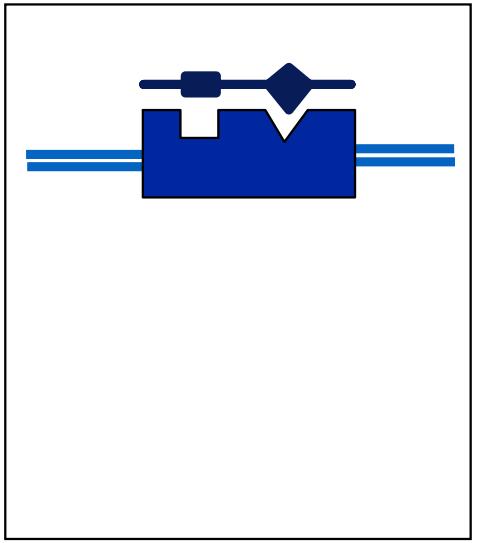
Attraction to the target

Potency

Efficacy

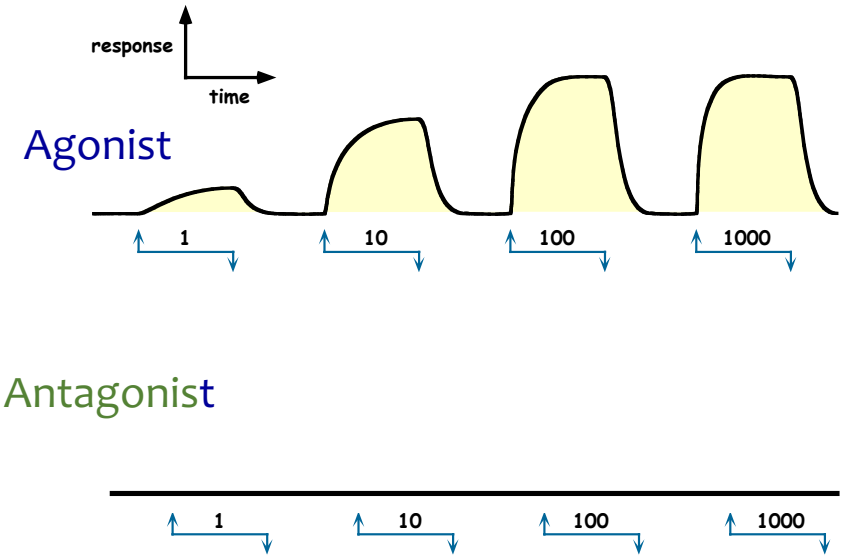
Antagonists

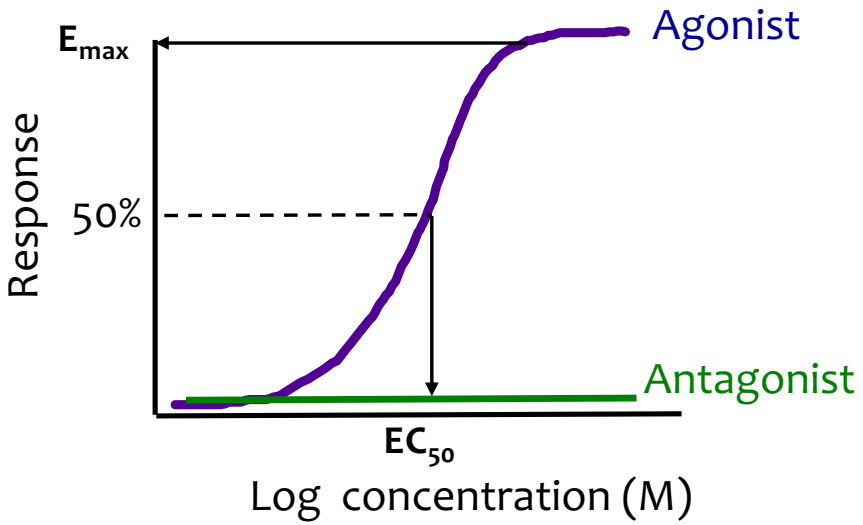
Bind and DO NOT
activate the receptor



The utility of the concentration-response curve

The concentration-response curve
Cellular / tissue responses





- **E_{max}** - measure of the **efficacy** of a drug (*How much effect?*)
- **EC_{50}** - measure of the **potency** of a drug (*How much drug?*)

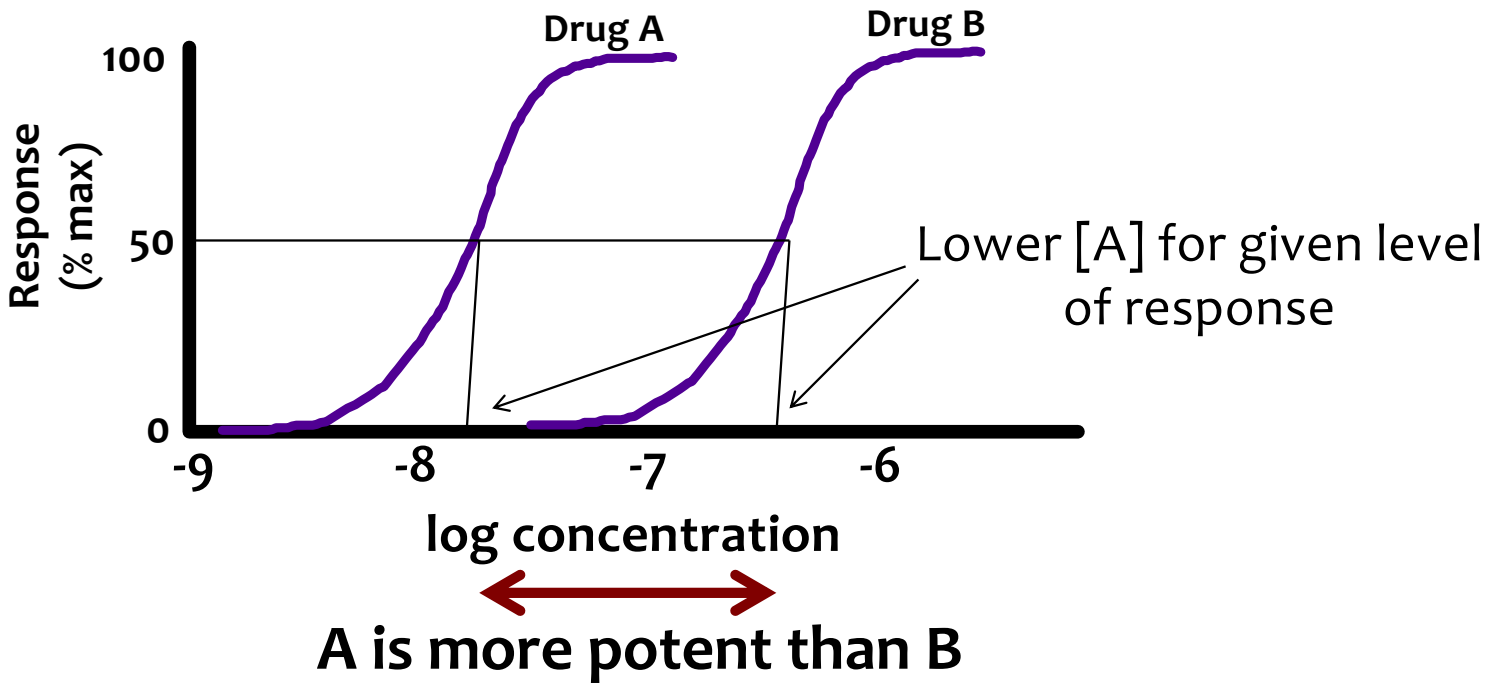
Antagonist unable to elicit response *in vitro* (no efficacy or potency?), but …

Antagonists CAN elicit responses in the body

- Effect only observed when agonist is acting at receptors
- Prevent receptor activation by endogenous chemicals when a system is active
  - Examples
    - Atropine blocks acetylcholine receptors
    - Propranolol blocks noradrenaline receptors
- Active *in vivo*
  - Dose-response can be elicited
  - Measurable potency & efficacy
- Important therapeutic drugs with clinical efficacy and potency

Potency (EC_{50})

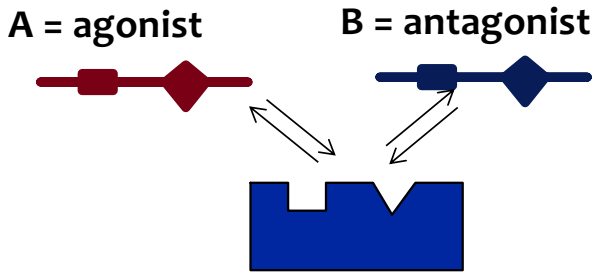
- How much drug is needed for effect
  - NOT the affinity
  - NOT the size of the response



Determining antagonist potency

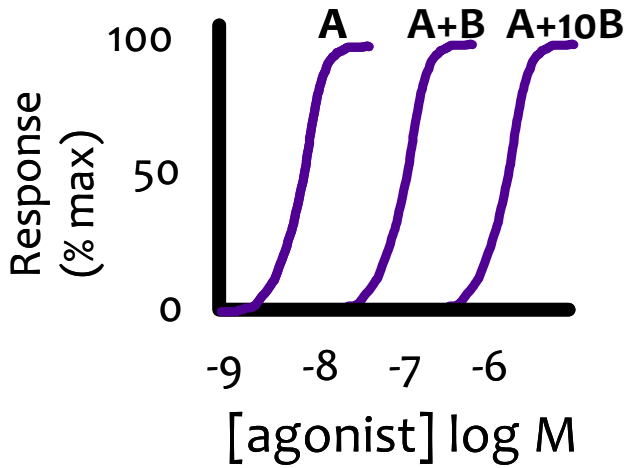
2 drugs acting at 1 receptor

- Assume mass action, reversible binding to receptor



At equilibrium

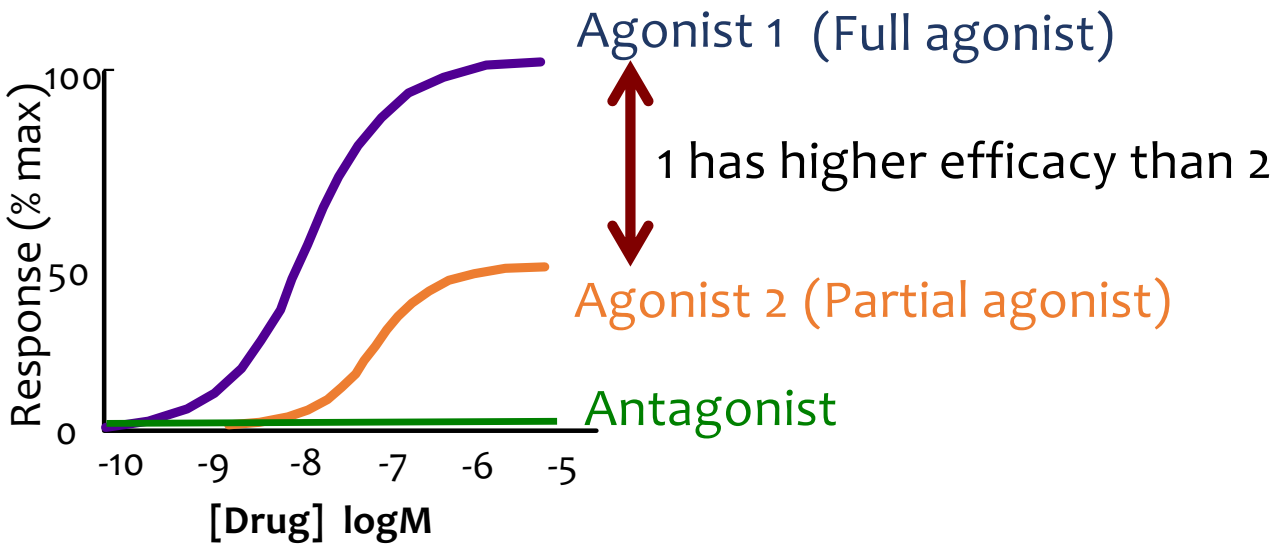
- The effect of the antagonist is to decrease the apparent potency of the agonist
- The relative shift the agonist concentration-response curve is a measure of antagonist potency
  - (pA_2 / pK_B)
- Surmountable / competitive
  - no change in agonist maximum
  - parallel shift in concentration-response curve



Efficacy (E_{max})

How much of an effect the drug can elicit

- Ability of a drug to activate the receptor
  - Agonist c.f. antagonist

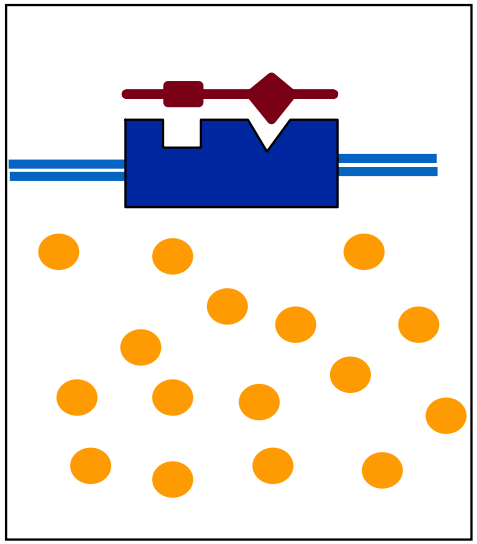


- Different maximal responses for drugs acting at same receptor
  - Full and Partial agonists

Drug action at receptors

Agonists

Bind and
activate the receptor



Used to mimic endogenous signaling molecules

Measurable property

Affinity

Attraction to the target

Potency

Amount required to have an effect

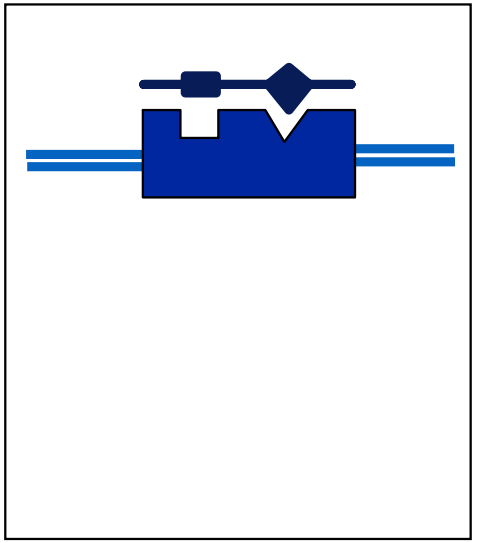
Efficacy

Only agonists elicit a cellular / tissue response

Intrinsic ***Clinical***

Antagonists

Bind and DO NOT
activate the receptor



Used to inhibit endogenous signaling molecules

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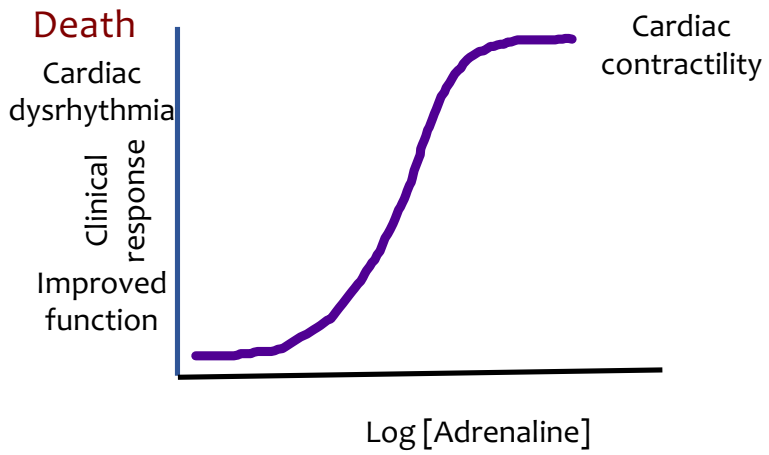
- Describe the importance of the concentration-response curve in characterising the action of drugs
- **Describe processes by which the body may influence the actions of a drug (Pharmacokinetics)**

All drugs have more than one action

- Drugs elicit responses in the body by interacting with molecular targets for endogenous molecules
  - Agonists mimic the endogenous molecules
  - Antagonists block the endogenous molecules
- Bigger response isn't always better

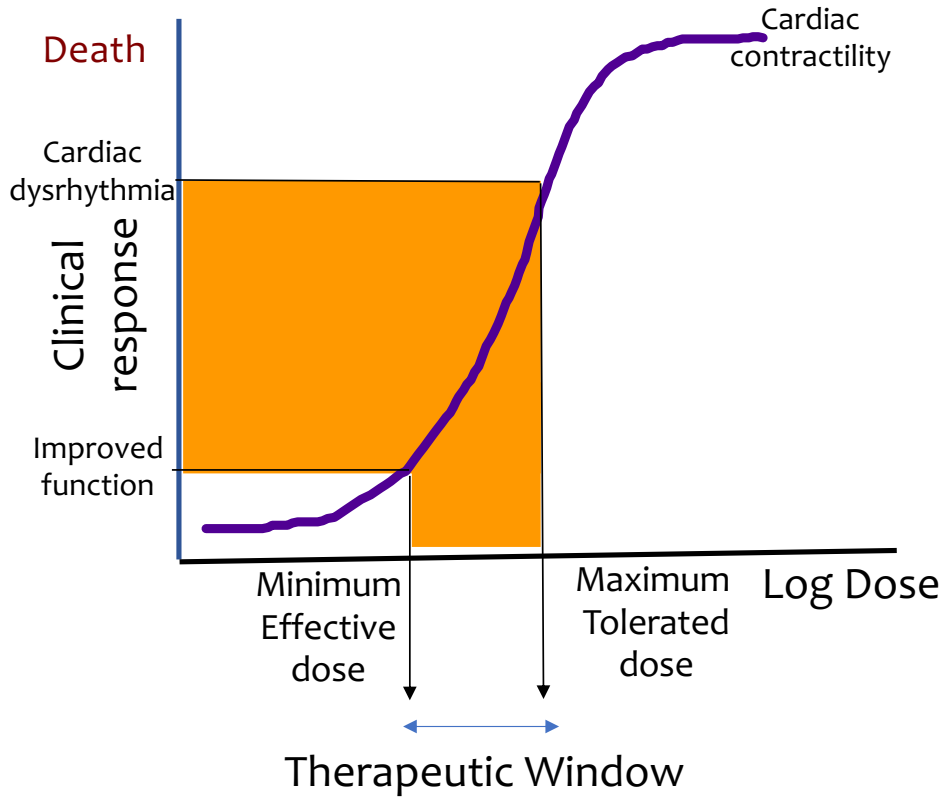


Optimize the benefit *(clinical efficacy)* & minimise the risk *(clinical toxicity)*.

Pharmacodynamics: clinical consideration

Adrenaline identical molecular target for therapeutic and toxic actions

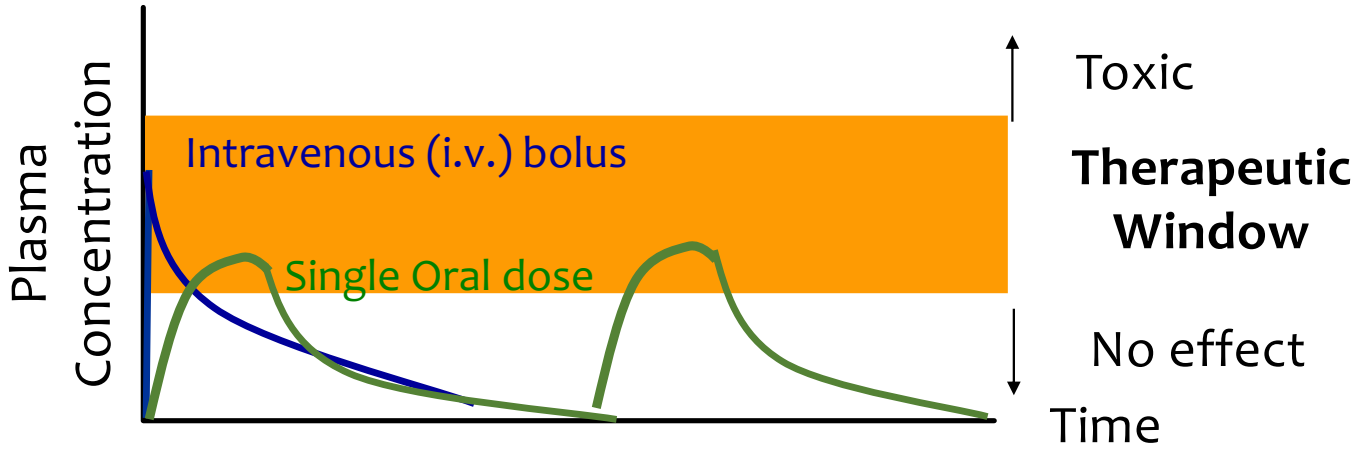
- *cardiac β1-adrenoceptor*



The usable dose of a drug is constrained by unwanted actions

Therapeutic challenge

Achieving and Maintaining the dose in the therapeutic window

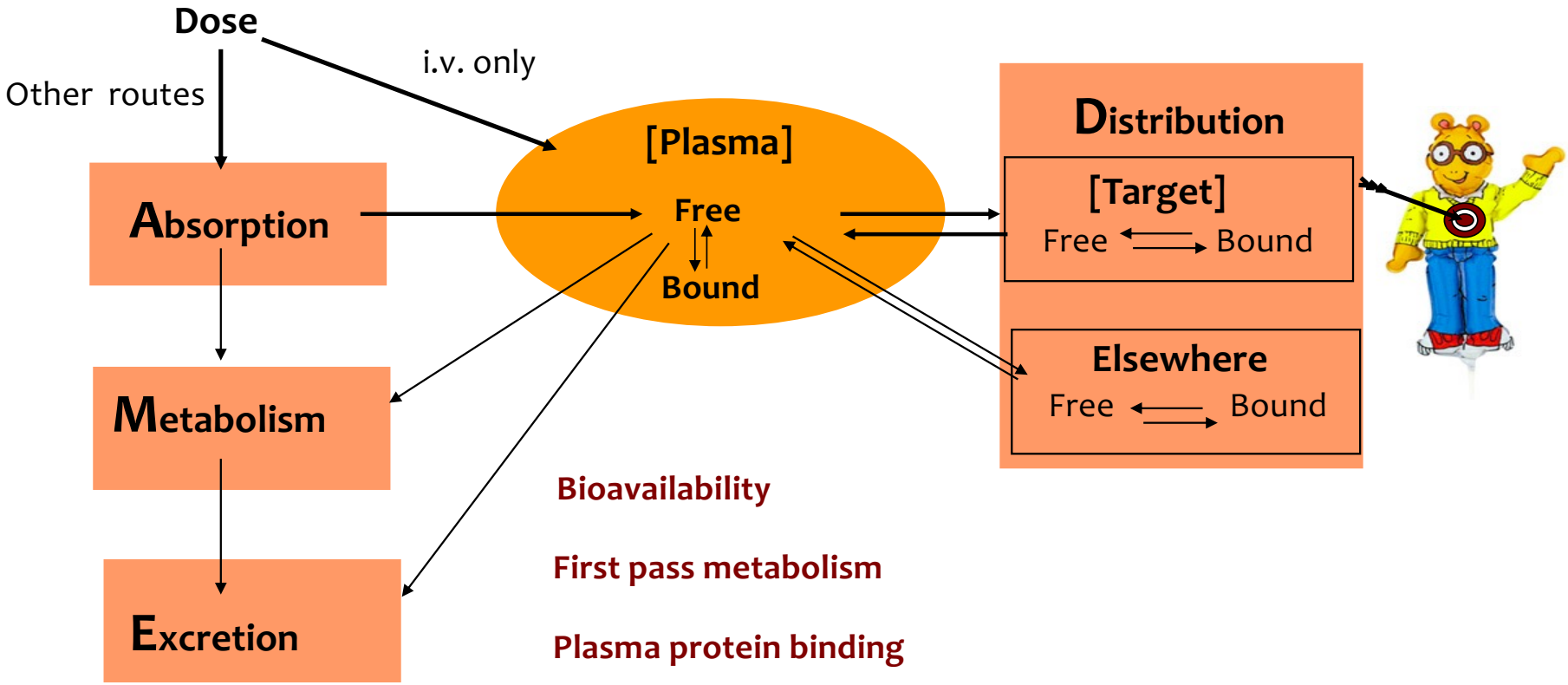


How & how much to give initially?

When to give the next dose?

Pharmacokinetics (ADME)

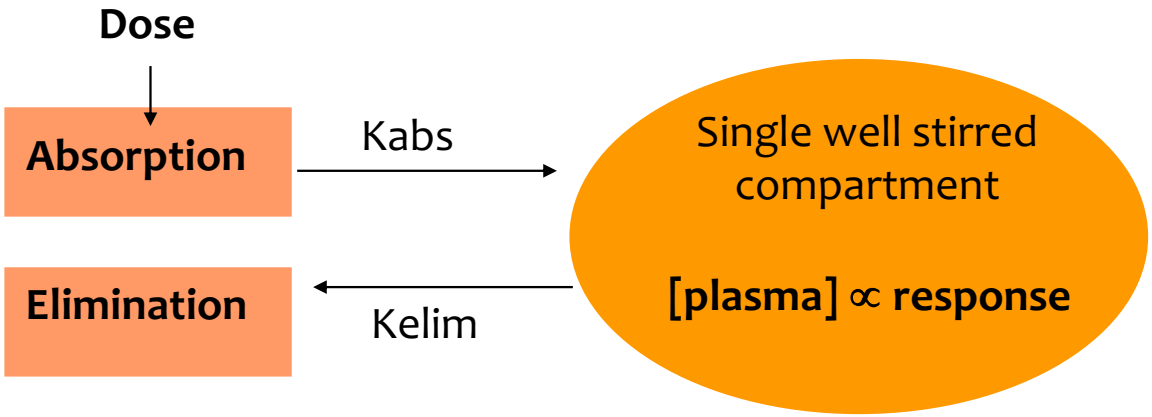
Processes influencing dose-concentration relationship



Affect how much but not how often!

Pharmacokinetics (ADME)

Equilibria can simplify to …



Parameters informing how often:

- **Volume of distribution (Vd)**
- **Clearance (Cl)**
- **Half-life ($t_{1/2}$)**

Safe and effective drug use

- application of pharmacological principles

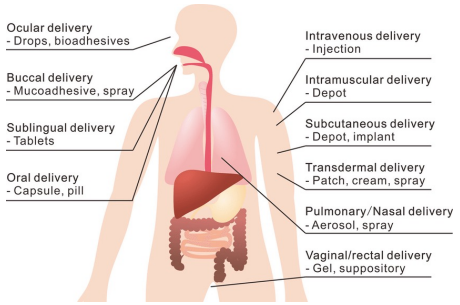
Pharmacodynamics **Pharmacokinetics**

Where ? How much ? How often ? How given ?

Affinity & selectivity

Potency & efficacy

Absorption
Distribution
Metabolism
Excretion



http://www.nationalpain.com/routes-of-administration

Clinical reasoning skills

Understanding of chemical signalling mechanisms

- In the sick patient drug action will depend upon:
  - Target distribution / function
    - Pathophysiological changes
  - Organ system response
    - Reflexes
  - Idiosyncrasy
    - Genetics

Application of pharmacological principles

- Pharmacodynamics and pharmacokinetics
  - Drug & dose should be tailored for the individual
    - Personalised medicine

Summary: Principles of Drug Action

Drugs affect living things

- Agonist or antagonist activity

Safe drug use

- Recognise the appropriate molecular drug targets
- Anticipate cellular / tissue / system / body effects
- Evaluate Benefit v Risk
  - Be aware of alternatives
- Quantify drug activity
  - Pharmacodynamics (PD)
    - Effect of drug on body
  - Pharmacokinetics (PK)
    - Effect of body on drug

WHOLE BODY Homeostasis Nerves/hormones
SYSTEMS Cardiovascular/ Renal /CNS
TISSUES Blood vessel/heart
CELLS Single/culture
MEMBRANES
MOLECULES Specific targets
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