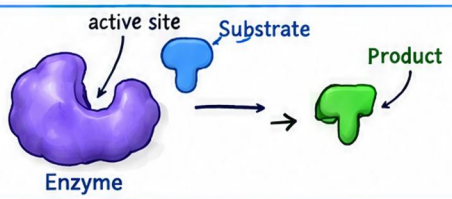
Enzyme inhibition

Look-alikes, saboteurs and killers - how drugs and poisons switch enzymes off

Dr. PP's i-Notes



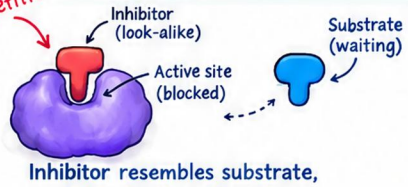
Enzyme inhibitor = a substance that _____ the rate of an enzyme-catalysed reaction.

Enzyme inhibition

- **Reversible**
  - Competitive
  - Non-competitive
  - Uncompetitive
- **Irreversible**
  - Covalent
  - Suicide inhibition
- **Allosteric**
  - Feedback

Competitive

Look-alike = competitive

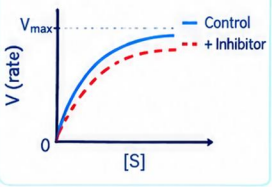


Inhibitor resembles substrate, fights for the active site.

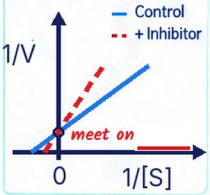
Km _____, **Vmax** _____

_____ by excess substrate.

Michaelis-Menten



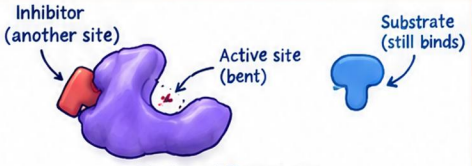
Lineweaver-Burk



Examples

- **Malonate** - _____
- **Statins** - _____
- _____ - dihydrofolate reductase
- **Sulfonamides** - dihydropteroate synthase
- _____ - vitamin K epoxide reductase

Non-competitive

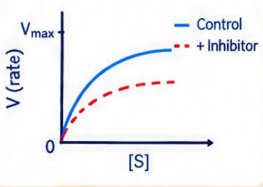


Binds a different site, changes enzyme shape.

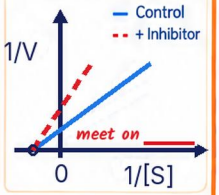
Km _____, **Vmax** _____

___ reversed by excess substrate.

Michaelis-Menten



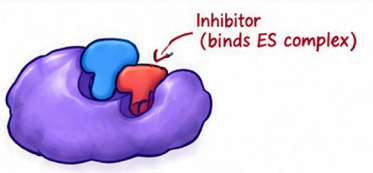
Lineweaver-Burk



Examples

- **Cyanide** - _____
- **Fluoride** - _____
- **Lead and mercury** - enzymes with ___ groups

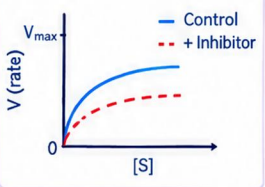
Uncompetitive



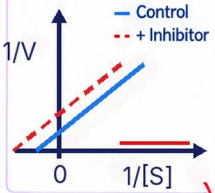
Binds only the ES complex.

Km _____, **Vmax** _____

Michaelis-Menten



Lineweaver-Burk



Examples

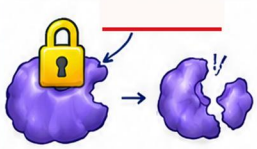
both down, lines parallel!

- _____ - placental alkaline phosphatase
- _____ - inositol monophosphatase (bipolar disorder)

Competitive changes ___, Non-competitive changes ___.

Feature	Competitive	Non-competitive	Uncompetitive
Binds to -			
Km			
Vmax			
Excess substrate reverses?			
Lineweaver-Burk lines			

Irreversible inhibition



_____

Enzyme permanently dead.

Recovery needs _____

Examples

- **Organophosphates** (malathion, parathion) - _____
- **Aspirin** - _____
- **Penicillin** - _____
- **Disulfiram** - _____

Suicide inhibition (mechanism-based)

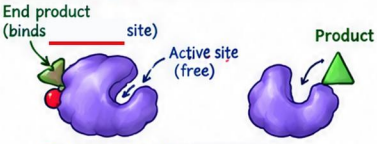


Enzyme converts harmless drug to a reactive trap.

Examples

- **Allopurinol** → _____ xanthine oxidase - gout
- **5-Fluorouracil** → FdUMP - _____ cancer
- **Clavulanic acid** - _____

Allosteric (feedback) inhibition



End product binds a _____ site away from the active site.

Example

- **CTP** inhibits _____ - details in regulation of enzymes.

VIMP: Competitive - Km _____, Vmax _____. Non-competitive - Km _____, Vmax _____.

Why does a fluoride vial keep blood glucose stable? Fluoride blocks enolase, so RBCs stop using glucose.

Recap: Lineweaver-Burk lines on y-axis = _____ on x-axis = _____ parallel = _____.

Methanol (hooch) poisoning: give _____ or fomepizole - they compete for alcohol dehydrogenase.

Organophosphate poisoning: atropine + pralidoxime early, before aging of the enzyme.

VIMP Types of enzyme inhibition with examples and graphs

Caution Higher Km means ____ affinity

Recap Irreversible = covalent, needs new enzyme

Exam pearl Statins are _____ inhibitors of HMG-CoA reductase

Therapeutic importance of enzymes

Enzymes as medicines, enzymes as drug targets, enzymes as poison targets

Dr. PP's i-Notes

enzyme as target

Most drugs work by blocking an enzyme



Enzyme

- **Penicillin** - ____
- **Sulfonamides** - ____
- **Trimethoprim** - bacterial
- **Zidovudine** - ____
- **Statins** (atorvastatin) - ____ - lower LDL cholesterol
- **Enalapril, ramipril** - ____ (ACE) - ____
- **Aspirin** - ____ (COX) - antiplatelet, pain, fever
- **Allopurinol, febuxostat** - ____ - ____
- **Omeprazole** - ____ (proton pump) - acid peptic disease
- **Acarbose** - ____
- **Sitagliptin** - ____ - ____ type 2 diabetes
- **Neostigmine** - ____ - ____
- **Disulfiram** - ____ - alcohol de-addiction
- **Methotrexate** - ____
- **5-Fluorouracil** - ____

VIMP: Clot busters work best when given early in myocardial infarction

Why is streptokinase not repeated? It is a bacterial protein – antibodies and allergy

Recap: streptokinase = enzyme as drug; statin = enzyme as target

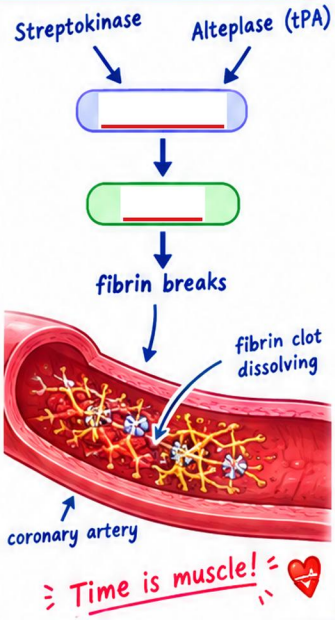
L-Asparaginase: leukaemic cells cannot make enough asparagine, normal cells can

Sitagliptin blocks DPP-4, so GLP-1 lasts longer and insulin rises after meals

Enzymes as medicines

enzyme as medicine

Enzyme	Therapeutic use
Streptokinase, urokinase, alteplase (tPA)	____ - acute myocardial infarction, pulmonary embolism; alteplase in ischaemic stroke
L-Asparaginase	____
Pancreatic enzymes (lipase, amylase, protease)	chronic pancreatitis, cystic fibrosis
____ (dornase alfa)	thins sticky sputum in cystic fibrosis
____	spreads local anaesthetic and subcutaneous fluids
Collagenase, papain	debridement of burns and ulcers
Trypsin-chymotrypsin	reduce ____ after injury and surgery
Lactase	____
____ (urate oxidase)	high uric acid in tumour lysis syndrome
Imiglucerase (glucocerebrosidase)	enzyme replacement therapy in ____ disease



Enzyme inhibitors as poisons

- **Organophosphate pesticides** ____
- **Cyanide** ____
- **Arsenic** ____ (lipoic acid)
- **Lead** ____ and ____ (anaemia)
- **Methanol** ____ makes formaldehyde and formic acid ____

VIMP - Enumerate therapeutic enzymes with uses

Caution - Alteplase is ____ streptokinase is not

Recap - Drugs and poisons often target the same enzyme

Exam pearl - ____ reactivates acetylcholinesterase

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