Allosteric Enzymes: Two Curious Puzzles

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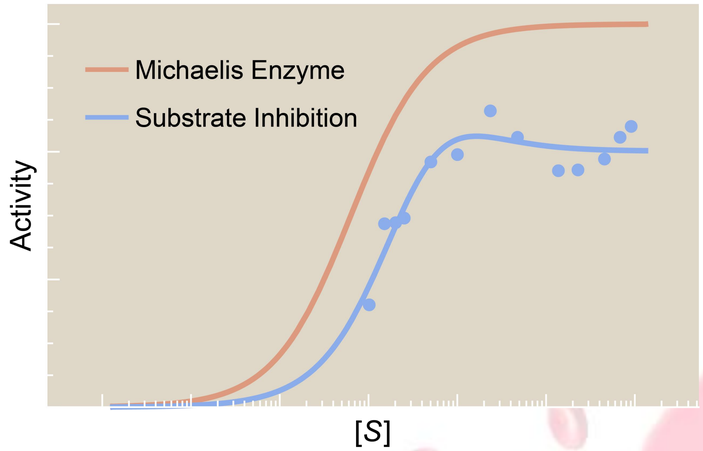
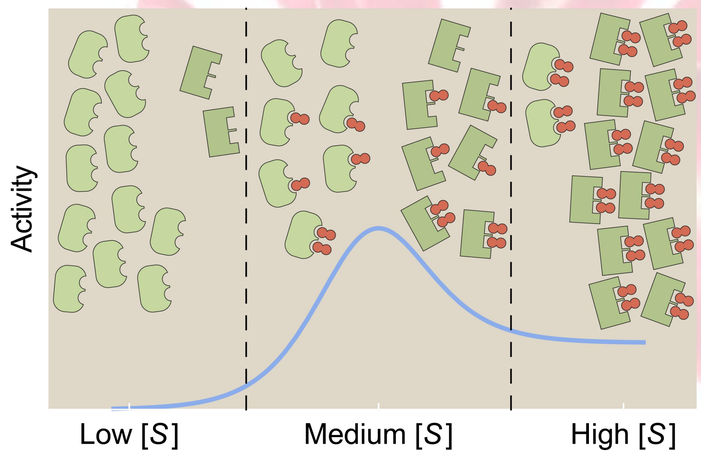
Substrate Inhibition



- **20% of enzymes** show substrate inhibition [1]
- We propose a **novel minimal mechanism** of substrate inhibition due solely to **allostery** and **multiple active sites**
- **Evidence** for this new mechanism underlying substrate inhibition found in **acetylcholinesterase** [2]

The Story

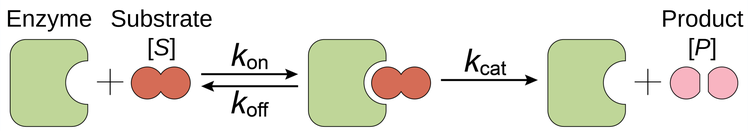


References

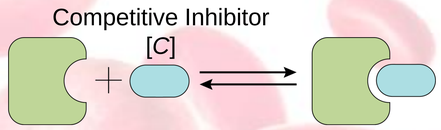
[1] Reed MC, Lieb A, Nijhout HF. Bioessays. 2010
[2] Changeux JP. Mol Pharmacol. 1966
[3] Mellinghoff IK, Sawyers CL. Springer Science and Business Media. 2012
[4] Wales ME, Madison LL, Glaser SS, Wild JR. J Mol Biol. 1999

Key Players

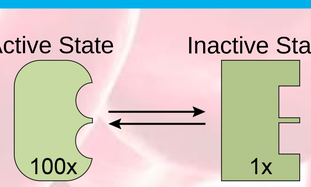
Enzyme + Substrate



Enzyme + Competitive Inhibitor



Allostery and Multiple Sites



- Enzyme switches between an active and inactive state
- Active state catalyzes substrate faster
- Two identical, independent substrate binding sites

Substrate Prefers Inactive

Substrate must have a Michaelis binding constant for the **inactive state** that is at least **twice as small**

Suspect Simple Stories

Substrate inhibition is more likely when the **unbound inactive state dominates** over the unbound active state

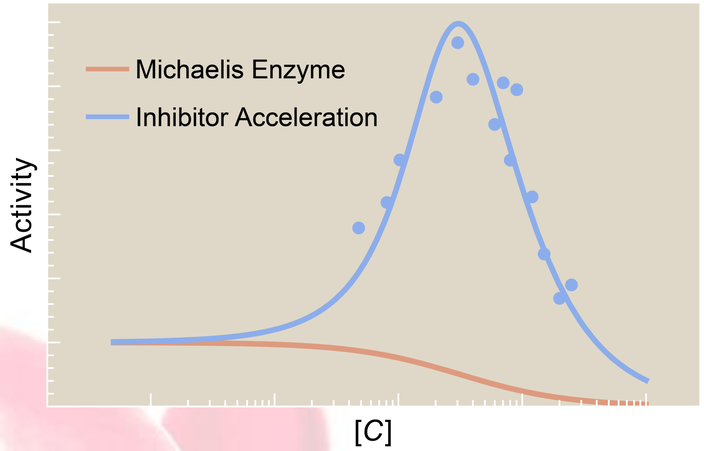
Enzyme Prefers Inactive

In the **absence of inhibitor**, enzyme must spend **more time in the inactive state** than the active state

Equal Inhibitor Affinity

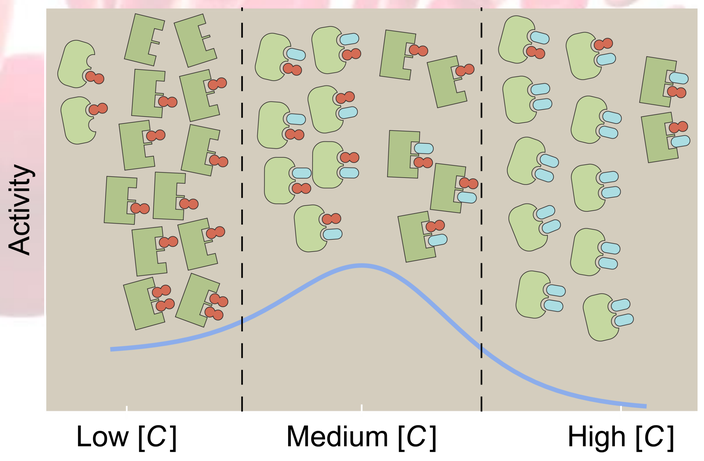
Inhibitor with **equal binding affinity** between **active and inactive states** can yield inhibitor acceleration

Inhibitor Acceleration



- Various **drugs** are competitive inhibitors of human metabolic enzymes [3]
- Known mechanisms of inhibitor acceleration rely on **allostery** and **multiple active sites** [4]
- Canonical example: **aspartate transcarbamoylase** (ATCase)

The Story



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