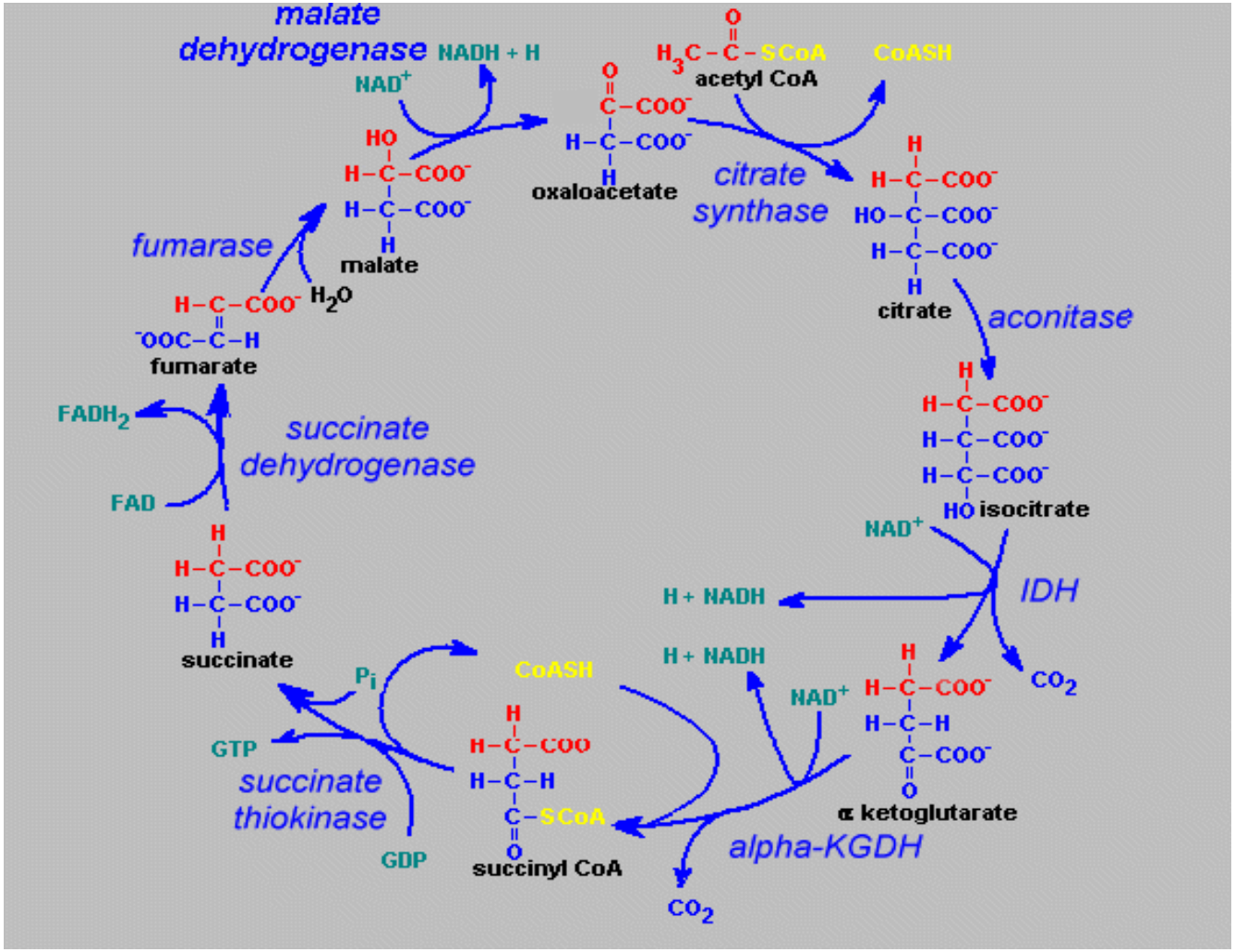
Inhibition

- Enzyme inhibitors are substances that reduce rate of reaction. Enzyme inhibitors are usually defined as substance that specifically affect the enzymatic mechanism. Substances that alter the enzyme's general environment, such as changes in pH, ionic strength or solvent are not usually considered inhibitors.

- Inhibitors are generally classified by their type of kinetic reaction mechanism, for example competitive inhibitors, suicide inhibitors, allosteric inhibitors, etc. Mathematical kinetic models have been developed for these various types of enzyme inhibition.

- In complex biological systems, inhibitors aid in controlling the activity and function of enzymes. This is important since living systems must tightly regulate their metabolic activity.

TCA cycle:
How are complex enzymatic processes controlled?



Competitive Inhibition

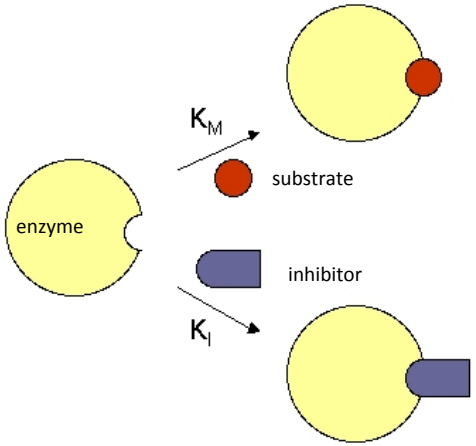
$E+S \Leftrightarrow ES \Rightarrow E+P \quad K_M = [E][S]/[ES]$

$+ \qquad K_I = [E][I]/[EI]$

I

⇳

EI



$[E_0]=[E]+[ES]+[EI]$

$= [E]+[ES]+[E][I]/K_I=[E](1+[I]/K_I) +[ES]$

Re-arranging

$[E]=([E_0]-[ES])/(1+[I]/K_I)$

Inserting into K_M equation above,

$K_M= [E][S]/[ES]=\{([E_0]-[ES])/(1+[I]/K_I)\}[S]/[ES]$

Competitive Inhibition

$K_M = ([E_0]-[ES])/(1+[I]/K_I)\}[S]/[ES]$

Re-arranging,

$K_M(1+[I]/K_I) = ([E_0]-[ES])[S]/[ES]$

Recall for M-M equation analysis,

$K_M' = ([E_0]-[ES])[S]/[ES]$

Substitute $K_M(1+[I]/K_I) = K_M'$

$v = V_M[S]/\{[S]+ K_M(1+[I]/K_I)\}$
$= V_M[S]/([S]+ K'_M)$ $\quad K'_M = K_M(1+[I]/K_I)$
note: $K_M' > K_M$

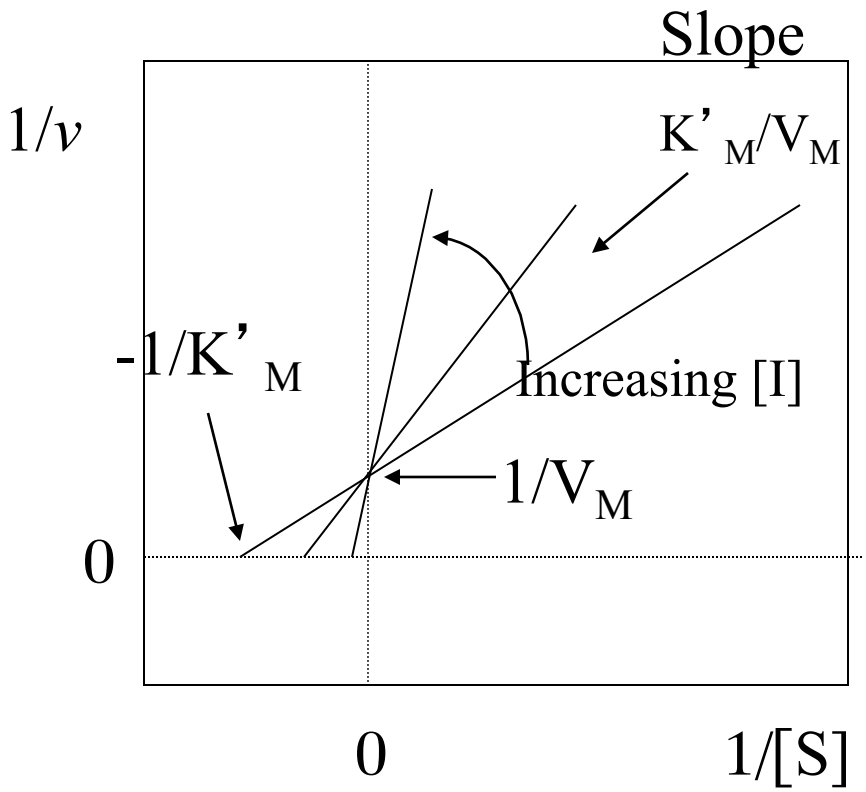
Using LB linearized plot,
$1/v = (K'_M/V_M)(1/[S])+ 1/V_M$

Determination of K_M and V_M

$v = V_M[S]/\{[S] + K_M(1+[I]/K_I)\}$
$= V_M[S]/([S] + K'_M)$

where $K'_M = K_M(1+[I]/K_I)$

Using LB linearized plot,
$1/v = (K'_M/V_M)(1/[S]) + 1/V_M$



Competitive Inhibition

I competes with S for E binding site

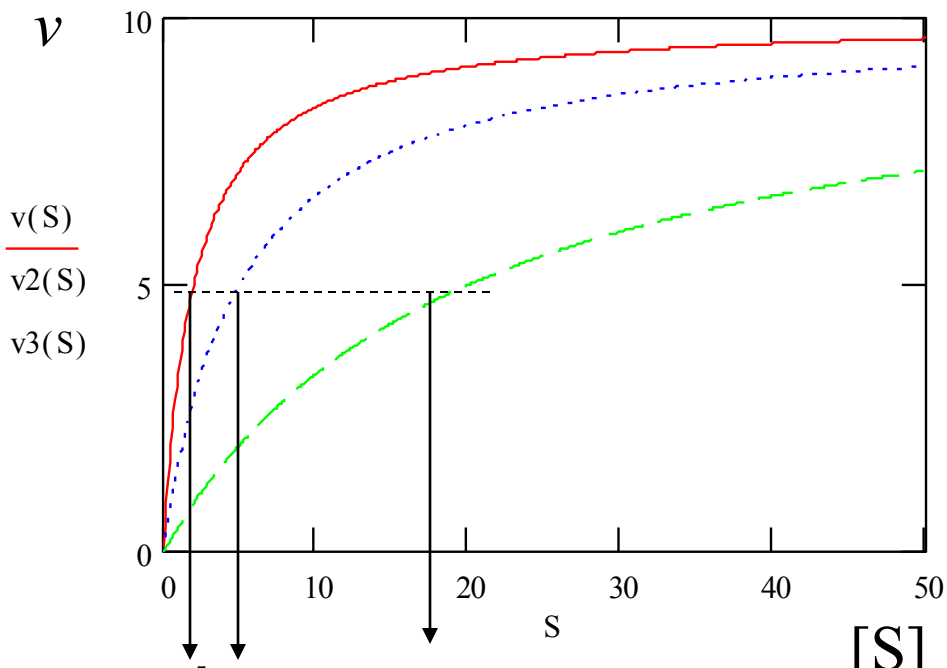
Competitive Inhibition

$v = V_M[S]/([S]+K'_M)$

Note:

V_M is unchanged

therefore can overcome inhibition by increasing [S]



K'_M increasing as [I] increases