Enzyme Regulation I
Enzyme Regulation Mechanisms

.1 Allosterism
.2 Covalent Modification
.3 Control of Synthesis
.4 Availability of Substrate
Control of Enzyme Activity

Substrate Does Not Change Enzyme Binding of Substrate

Substrate Does Change Enzyme Binding of Substrate

Allosteric Enzyme Kinetics
Control of Enzyme Activity

Homotropic and Heterotropic Effectors

- Sigmoidal curve
- Reaction velocity ($V_0$)
- [S]
- + Activator (ATP)
- Control (no ATP or CTP)
- + Inhibitor (CTP)
Control of Enzyme Activity

Aspartate Transcarbamoylase (ATCase)

Six Regulatory Subunits

Six Catalytic Subunits
Control of Enzyme Activity
Control of Enzyme Activity

Aspartate Transcarbamoylase (ATCase)

- Aspartate - Amino Acid
- ATP - High Energy, Purine
- CTP - End Product of Pathway
Control of Enzyme Activity

ATCase is Affected by One of its Substrates - Aspartate
Aspartate is a Homotropic Effector of ATCase

Binding of Aspartate by ATCase Favors the R-State
so Additional Substrate Binding is Favored
Control of Enzyme Activity
- Allosteric Control of ATCase

ATP Activates ATCase (Converts to R State)

In the Presence of ATP, the $V_0$ is Increased Compared to No ATP
Control of Enzyme Activity
• Allosteric Control of ATCase

CTP Reduces the Activity of ATCase - Converts to T State

$V_0$ Decreases as $[CTP]$ Increases
Control of Enzyme Activity

- Allosteric Control

Aspartate is a Substrate, but Neither ATP nor CTP is. All Affect the Enzyme

Six Catalytic Subunits - C1 to C6

Aspartate Binds to Catalytic Subunits Favors R State

ATP and CTP Bind Regulatory Sites
ATP Favors R State
CTP Favors T State

Six Regulatory Subunits - R1 to R6
Control of Enzyme Activity

- Allosteric Control

At Low [S], ATCase in T State

At High [S], ATCase Mostly in R State

As [S] Increases, ATCase Increasingly in R State

Allosteric Enzyme Kinetics

\[ V_0 \]
Control of Enzyme Activity

- Allosteric Control

Thus, ATCase is Most Active When Energy (ATP) is High and When Pyrimidines are Low in Concentration Relative to Purines

ATCase is Least Active When Pyrimidine Concentration (CTP) is High
Feedback Inhibition

• Aspartate Transcarbamoylase (ATCase)

\[ \text{Aspartate} \xrightarrow{\text{ATCase}} \text{Carbamoyl Aspartate} \xrightarrow{\text{Pi}} \text{Carbamoyl Phosphate} \]

- Cells in a High Energy State Have Lots of ATP Activates ATCase
- Cells With Abundant Amino Acids Have Lots of Aspartate Activates ATCase

\[ \text{Carbamoyl Aspartate} \xrightarrow{\text{ATCase}} \text{Multiple Reactions} \]

\[ \text{Multiple Reactions} \rightarrow \text{CTP} \]

- Accumulating CTP Inhibits Enzyme
Covalent Modification

- **Enteropeptidase**
  - Trypsinogen
  - Trypsin
    - Proelastase
    - Elastase
    - Procarboxypeptidase
    - Carboxy-peptidase
      - Chymotrypsinogen
      - Chymotrypsin
      - Prolipase
      - Lipase
Covalent Modification

1. Binding of Hormone to Receptor
2. Activation of G Protein by Receptor
3. Activation of Adenylate Cyclase by G Protein
4. Synthesis of cAMP
5. Activation of Protein Kinase A by cAMP
6. Phosphorylation by Protein Kinase A
   Activates Phosphorylase Kinase
7. Phosphorylation of
   Phosphorylase b → a (activates)
8. Phosphorolysis of Glycogen
Control of Enzyme of Activity

- Covalent Modification Control

Chymotrypsinogen (Inactive)

1

Trypsin

PeptideBondBroken

π - Chymotrypsin (Partly Active)

15 16

π - Chymotrypsin

α - Chymotrypsin (Fully Active)

1 13 16

π - Chymotrypsin

146 149

π - Chymotrypsin

Peptide Bonds Broken, Tripeptide Released

Peptide Bond Broken, Dipeptide Released
Control of Enzyme of Activity

- Zymogens

- Protease Precursors
  - Pepsinogen
  - Proenteropeptidase
  - Trypsinogen
  - Chymotrypsinogen
  - Procarboxypeptidases
  - Blood Clotting Proteins
  - Procaspases
  - Proelastase

- Other
  - Pacifastin
  - Plasminogen
  - Angiotensinogen
  - Prolipase
  - Pre-proinsulin

http://www.ebi.ac.uk/
Control of Enzyme of Activity
• Other Covalent Modifications to Proteins

• Phosphorylation - Kinase Cascades
• Acetylation - Histones
• Formylation - All Prokaryotic Proteins
• Acylation - Anchored Membrane Proteins (SRC)
• ADP Ribosylation - Transcription Factors
• Prenylation - Ras
• Sulfation - Serine Protease Inhibitors
• Ubiquitination - Many Proteins
• γ-Carboxylation - Clotting Proteins
Control of Enzyme of Activity

• γ-Carboxylation

Glutamate Side Chain   →   γ-carboxyglutamate

Carboxyl Group Added