Enzyme Regulation

Enzyme Regulation

Recall that enzymes have 4 major attributes:

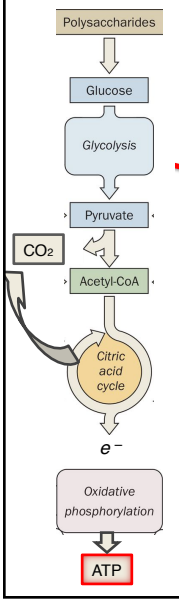
1. Increase rates of chemical reactions
2. Catalysis under mild conditions of temperature and pH
3. Very specific binding to substrates
4. Can regulate their activity

Control of Enzyme Activity

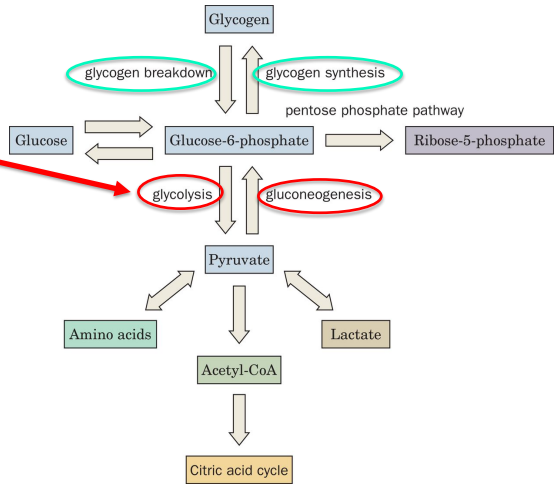
EXAMPLE:

Enzyme Regulation

Overview of Catabolism



Interconnected and opposing pathways:

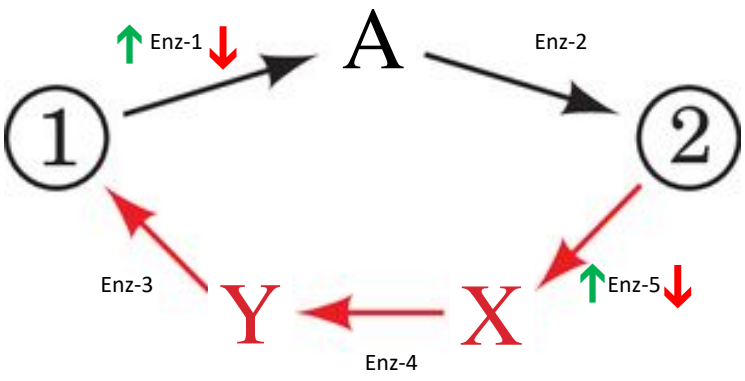


How are these opposing pathways regulated so that they are not working at the same time in a futile cycle?

EXAMPLE:

Enzyme Regulation

First: Catabolic & Anabolic Pathways Differ



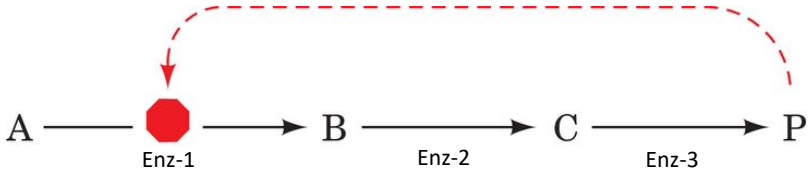
Second: Give an enzyme specific for each pathway an on/off switch

If you need ① → ② to happen, activate Enz-1 and inactivate Enz-5
If you need ② → ① to happen, reverse the controls.

EXAMPLE:

Enzyme Regulation

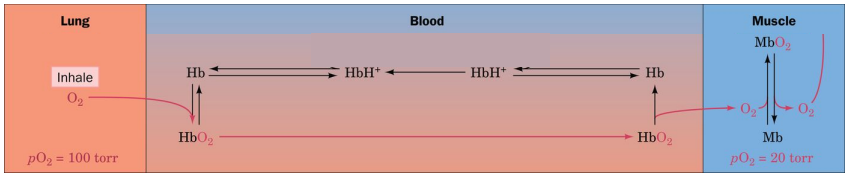
How do you design this switch?



- **This on/off switch is normally at the start of a pathway so all the intermediates need not be made; i.e., at the committal step.**
- **This on/off switch is often controlled by a small molecule, often the product of the pathway; i.e., Negative Feedback Regulation**

Enzyme Regulation

Another Example (not just for enzymes)**:**
Hemoglobin & Myoglobin
in O_2 Transport



Hb has high affinity = ON

Hb has low affinity = OFF

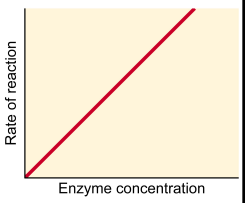
Enzyme Regulation

So, how are cellular processes controlled?

These controls are everywhere, from simple binding/release to embryological problems that set into motion all the processes to take a fertilized egg to an embryo.

THERE ARE THREE BASIC STRATEGIES:

1. Genetic Control
2. Covalent-Modification Control
3. Allosteric Control



Speed of each type of control:
Slow (minutes)

Enzyme Regulation

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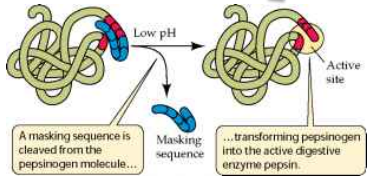
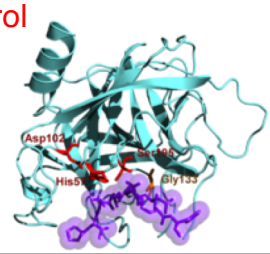
1. Genetic Control
2. Covalent-Modification Control
3. Allosteric Control

Speed of each type of control:
Medium (seconds)





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THERE ARE THREE BASIC STRATEGIES:

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Speed of each type of control:
Fast (msec)

Enzyme Regulation

Control by Covalent Modification:

Proteolytic activity
Phosphorylation
Adenylation
etc.
Methylation

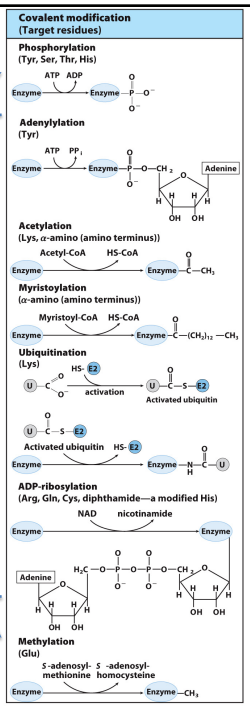


Figure 6-36

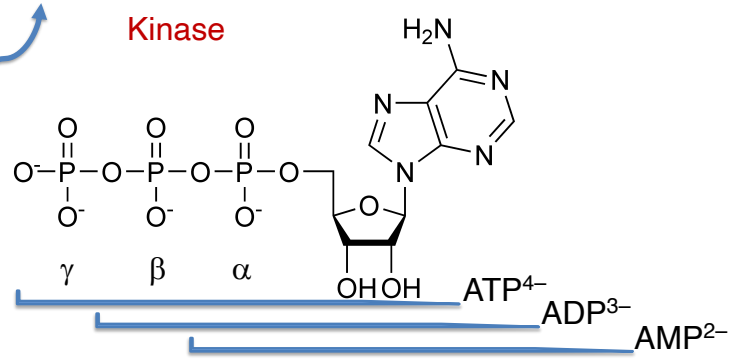
Enzyme Regulation

Control by Covalent Modification:
Phosphorylation

$ATP^{4-} + R\text{-}OH \rightleftharpoons ADP^{3-} + R\text{-}O\text{-}PO_4^{2-} + H^+$

Kinase

Now, if R = an enzyme



Enzyme Regulation

Control by Covalent Modification:

$ATP^{4-} + Protein\text{-}OH \rightleftharpoons ADP^{3-} + Protein\text{-}O\text{-}PO_4^{2-} + H^+$

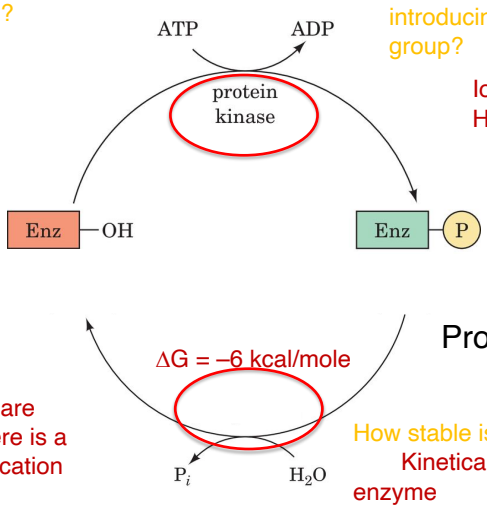
Protein Kinase

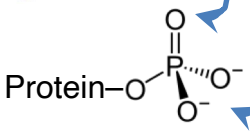
What R-groups?

Ser, Thr, Tyr

What are the effects of introducing a phosphoryl group?

Ionic environment
H-bond acceptors

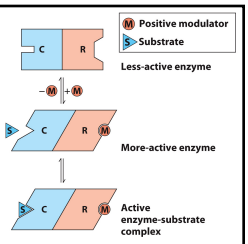




Because enzymes are involved in this, there is a potential for amplification

How stable is this modification?
Kinetically stable; requires an enzyme

Enzyme Regulation



Control by Covalent Modification:

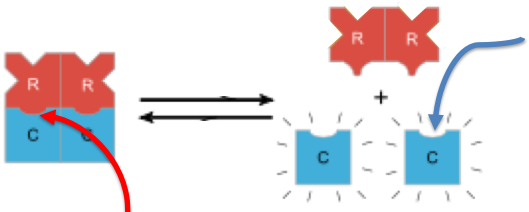
EXAMPLE: Protein Kinase A

AKA: cAMP-dependent Protein Kinase

$\alpha_2\beta_2$ (90 kDa & 40 kDa)

α is Regulatory (R)

β is Catalytic (C) and has the kinase activity



Inactive Active

The active site recognizes a particular site on substrate proteins
Target sites have the consensus sequence:
$R^B_K XSB$

small Large hydrophobic

Why is PKA inactivated when bound to R_2?

R has a sequence: RRGAI that fits into the C active site!

How is this equilibrium shifted? Cyclic-AMP (cAMP)