Fatty acyl – CoA

Camitime acyl
Transferase

Fatty acids are activated by an enzyme, fatty acyl-CoA synthetase to produce fatty acyl-CoA, a reaction that occurs in the cytoplasm. The β-oxidation of fatty acid occurs inside the mitochondrion. Therefore, the fatty acyl-CoA has to traverse the mitochondrial membranes. The inner mitochondrial membrane is not permeable to fatty acul-CoA; to overcome this barrier, fatty acyl-CoA is converted into fatty acyl-carmitone by the enzyme carmitine acyltransferase. Fatty acyl-carnitine is able to traverse the embrane and on getting into the mitochondrion, is converted back to fatty acyl-CoA and thus provides substrate for β-oxidation. Thus, variations in (carnitone) could regulate the rate of fatty acid oxidation without affecting other metabolic processes.

Another, e.g. of control by cofactor availability is the regulation of e-transport and oxidative phosphonylation in the nito-chondria by adenine nucleotides.

(a) Product removal – If a pathway substrate is converted to the pathway product by a series of reactions, the removal of the product could control the rate of its formation from the substrate. Minor pathways or perhaps specific portions of metabolic pathways may be controlled by such a mechanism. A typical, e.g. is the conversion of pynivate to lactate in muscle catalysed by lactate DH and the movement of lactate from the muscle to the blood. An increased blood flow through the muscle will increase the rate of lactate removal from the muscle which could therefore increase the rate of conversion of pyruvate to lactate. Another possible, e.g. is the utilization of acetoacetic acid by extra-hepatic tissues.

(1) The second level of control of metabolic pathways is through the action of regulatory enzymes. There are 2 major types of regulatory enzymes:

(a) Allosteric enzymes: These are enzymes whose catalytic activity is modulated through the non-covalent binding of a specific metabolite at a site on the protein other than the catalytic site;

(b) Covalently modulated enzymes: These are enzymes that are inter-converted between active and inactive forms by the action of other enzymes. They also respond to non-covalent allosteric modulators. The 2 types of regulatory enzymes respond to alterations in the metabolic state of a cell or tissue on a relatively short time scale – allosteric enzymes within seconds and covalently regulated enzymes within minutes.

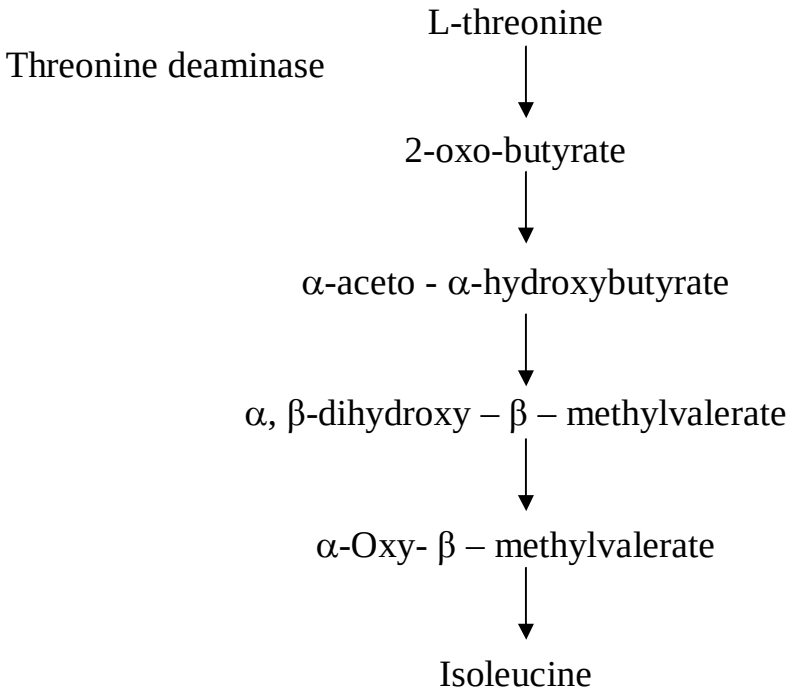
(a) Allosteric enzymes.

Allosteric regulation acts to modulate enzymes situated at key steps in metabolic pathways. IN metabolic pathways, the end product of the reaction sequence may inhibit an enzyme at or near the beginning of the sequence; such that the rate of the entire pathway is determined by

the steady-state concentration of the end-product. Consider the reaction sequence:

$$A \xrightarrow{E_1} B \xrightarrow{E_2} C \xrightarrow{E_3} D \xrightarrow{E_4} G$$

In this scheme, G represents an essential metabolite (lipid, protein, nucleotide). Here, G, the end-product inhibits the 1st step in the reaction sequence catalysed by E_1. Therefore, when sufficient G is synthesized, it blocks further synthesis of itself. This phenomenon whereby product of a reaction sequence inhibits the activity of an enzyme early in the biosynthetic pathway is referred to as feedback inhibition or feedback regulation or end-product inhibition. The 1st enzyme in this sequence that is inhibited by the end product is called an Allosteric enzyme. The reaction catalysed by the allosteric enzyme is usually irreversible under intra-cellular conditions. It is often called the committing reaction or the rate-limiting step; once it occurs all the ensuing reactions of the sequence will take place. Typical eggs include regulation of biosynthesis of amino acids and puries in micro-organisms. IN the synthesis of L-isoleucune from L-threonine, ile inhibits the 1st enzyme in the pathway, threonine deaminase

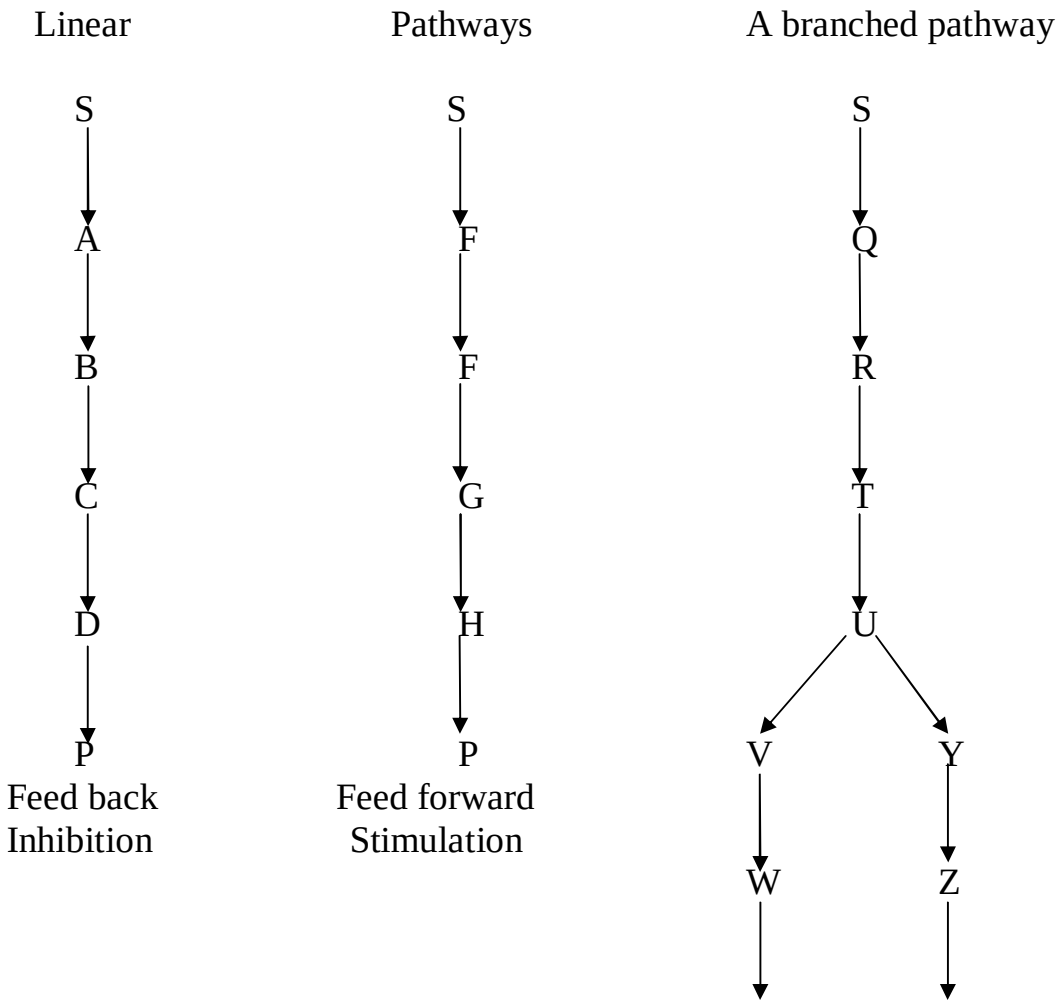


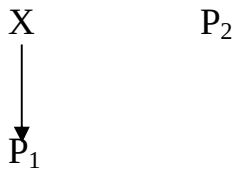
In the synthesis of cytidine triphosphate (CTP) from carbamyl PO_4 + L-aspartrate, CTP inhibits aspartate, trans-carbamylase. It is a good strategy for the cell to regulate a metabolic pathway at its 1st step, to achieve maximum economy of metabolites.

Patterns of allosteric modulation

Draw diagrams of linear and branched pathways – see next page.

In linear pathways, the end-product usually inhibits the 1st enzyme in the sequence. Sometimes, the 1st substrate or the precursor may act as a +ve stimulator and stimulate the 1st reaction. IN branched pathways the metabolite at the branch point is often the feed-back inhibitor of the 1st enzyme, whereas the 2 end-products of the branches (P_1 & P_2) often act as feedback, inhibitors of the 1st enzyme after the branch point.




X
P2
P1