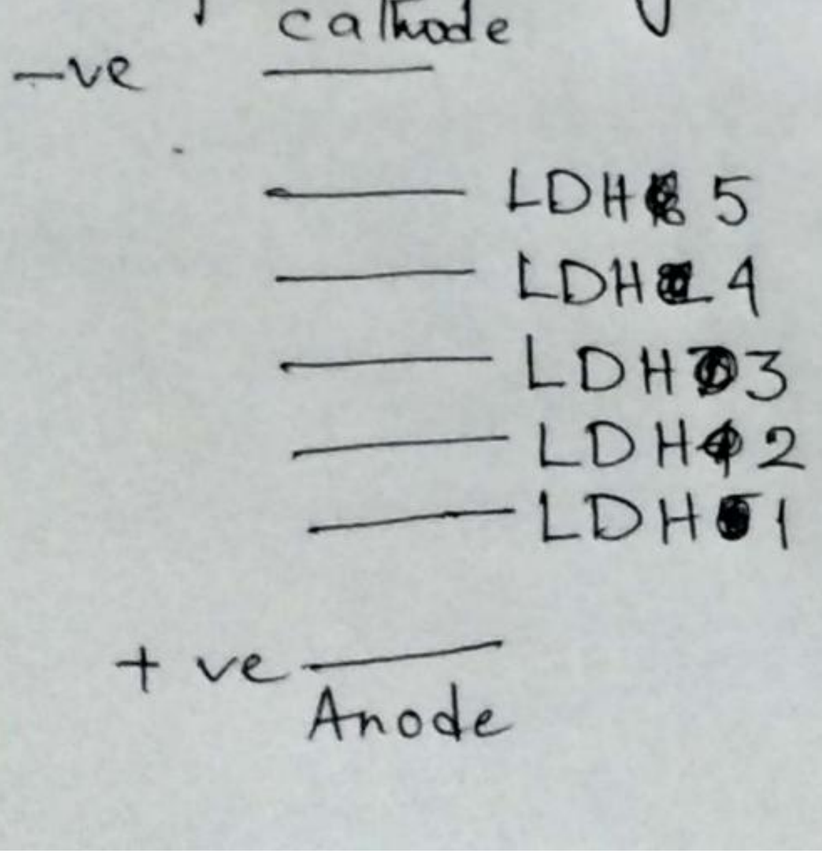
Regulation of Enzyme activity by Isozyme

As we have discussed earlier that enzymes can be controlled by various ways so that their function at proper time and place. One of such control is mediated by Isozyme. Isozymes are different enzymes catalyze the same reaction. Isozymes provide an avenue for varying regulation of the same reaction at distinct locations or times to meet the specific physiological needs in a particular tissue. They are homologous enzyme within a single organism, catalyze the same reaction but differ in structure, K_M, Vmax values and regulatory properties. One such example is Lactate dehydrogenase enzyme (LDH)

LDH catalyzes the reversible ox-red reaction

$$\text{Lactate} + NAD^+ \underset{LDH}{\overset{LDH}{\rightleftharpoons}} \text{Pyruvate} + NADH + H^+$$

LDH occurs in animals as five different isozyme separable by electrophoresis



All the LDH isozyme contain 4 polypeptide chains each with M.W. 33,500. But the five isozymes contain varying ratios of two kinds of polypeptides which differ in composition and sequence.

The A chains (also designated M for muscle) and B chains (designated H for heart) are coded by two different genes. In skeletal muscle the LDH1 isozyme that predominates and contain 4 A chains, and in heart the predominant isozyme contains four B chains. The LDH isozymes in other tissues are a mixture of the five possible forms (e.g A_4, A_3B, A_2B_2, AB_3 and B_4). The different lactate dehydrogenase isozymes differ significantly in the Vmax & KM values particularly for pyruvate.

The properties of LDH isozymes A_4 favor rapid reduction of very low conc. of pyruvate to lactate in skeletal muscle whereas isozyme B_4 favour rapid oxidation of lactate to pyruvate in heart. The other LDH isozymes have intermediate kinetic properties.

Many different enzymes involved in cell metabolism have been found to occur in multiple isozyme forms. All the isozymic form of a given enz catalyze the same reaction but differ in kinetic properties and may also differ in their response to allosteric modulators.

LDH being a tetramer, can combine in different proportion (H form and M form)

Type of Isozyme	Composition	Location	Electrophoretic mobility
LDH1	HHHH	Heart & Erythrocyte	Fastest
LDH2	HHHM	Heart & Erythrocyte	Faster
LDH3	HHMM	Brain & Kidney	Fast
LDH4	HMMM	Skeletal muscle & Liver	Slow
LDH5	MMMM	Skeletal muscle & Liver	Slowest

The M_4 isozyme functions optimally in the anaerobic environment of hard working skeletal muscle, whereas H_4 isozyme does so in the aerobic environment of heart muscle.

Physiological significance of different forms of isozyme — The appearance of some isozymes in the blood is a sign of tissue damage and hence useful for clinical diagnosis. For instance, an increase in serum levels of H4 relative to H_3M H_3M is an indication that a myocardial infarction

or heart attack, has damaged heart muscle cells leading to the release of cellular material.

The distribution of the different isozyme forms of any given enzyme reflects ~~four~~ several factors e.g.

i) The differing metabolic patterns in different organs. For ex. the LDH isozymes in heart and skeletal muscle reflect the metabolic differences of these organs.

ii) Fine tuning of metabolic rates through the different responses of isozyme forms to allosteric modulators. Some regulatory enzymes occur in isozymes forms that differ in their response to modulators.

Other example of isozyme, glucokinase/hexokinase, isozymes of creatine phosphokinase. Creatine kinase or phosphokinase (CPK) catalyze the interconversion of phosphocreatine to creatine. CPK exists in 3 isozyme.

There are 6 isozyme of Alkaline phosphatase has been identified.