

ENZYME AS THERAPEUTIC AGENT

ENZYMES IN USED IN MEDICAL FIELD

Diagnostic indicators – The activities of many enzymes are routinely determined in plasma (rarely in tissue biopsies) for diagnostic purposes in diseases of the heart, liver, skeletal muscle, pancreas and other tissues - **enzyme diagnostics**

Therapeutic agents – several enzymes are used as drugs;
new approach – **enzymotherapy**

Diagnostic tools – use as chemicals in clinical laboratory

Examples of enzymes commonly assayed for therapeutic purposes

Enzyme	Location	Cause of elevated plasma level
Acid phosphatase - ACP	Prostate	Prostatic cancer
Alkaline phosphatase – ALP	Bone, liver	Rickets, hypoparathyroidism, osteomalacia, obstructive jaundice, cancer of bone/liver
Alanine aminotransferase – ALT	Liver (muscle, heart, kidney)	Hepatitis, jaundice, circulatory failure with liver congestion
Aspartate aminotransferase – AST	Heart, muscle, red cells, liver	Myocardial infarction, muscle damage, anemia, hepatitis, circulatory failure with liver congestion
Amylase - AM	Pancreas	Acute pancreatitis, peptic ulcer
γ -Glutamyl transferase – GMT	Liver, kidney, pancreas	Hepatitis, alcoholic liver damage, cholestasis

Examples of isoenzymes commonly assayed for therapeutic purposes

Enzyme	Location	Cause of elevated plasma level
Creatine kinase – CK		
CK-MB	Heart	Myocardial infarction
CK-MM	Skeletal muscle	Muscular dystrophy
Lactate dehydrogenase – LD		
LD ₁ > LD ₂	Heart, kidney, blood cells	Myocardial infarction, kidney disease, megaloblastic anemia, leukemia
LD ₂ , LD ₃		Leukemia
LD ₅	Liver, muscle	Liver disease, muscle damage

Healthy individuals - levels of intracellular enzymes fairly constant, low –

the rate of **enzyme release** from damaged cells into plasma **balanced** by the rate of **removal of enzyme** protein from plasma

Physiological enzyme levels \Rightarrow reference values of the enzyme activities.

Elevated enzyme activity in the plasma – reflect **tissue damage** accompanied by **increased release of intracellular enzyme**

Skeletal muscle during exertion – physiologically elevated levels of muscle enzymes in plasma

Many diagnostically important enzymes = isoenzymes – pattern of isoenzymes in plasma (determined electroforetically)

– a means of **identifying the damaged tissue**

ENZYMOTHERAPY

Orally administered enzymes – treatment of a variety disorders

- **digestive, gastrointestinal, pancreatic**
- **Inflammatory diseases, edema**
- **immune and autoimmune diseases**
(arthritis, multiple sclerosis)
- **viral diseases** (herpes, AIDS)
- **cancer**

Mixtures of enzymes of plant and/or animal **origin** **proteinases, amylase, lipase** - administered as acidoresistent tablets.

- **Pancreatin** – **trypsin, chymotrypsin, lipase, amylase**
- **Wobenzym** – pancreatic and plant proteolytic enzymes – **trypsin, chymotrypsin, papain** (Carica papaya), **bromelain** (ananas) =

combination of enzymes with **different specificity, pH optimum, stability, interaction with inhibitors and antiproteases**
⇒ **multiple action**

- **Substitution of missing production of digestive enzymes – digestive enzymes – pepsin trypsin...**
- **Removal of deposits of death tissue or fibrin (e.g. in lungs, eyes), treatment of skin defects – proteinases, nucleases, collagenase**
- **Acceleration of fibrinolysis in lungs embolization (activation of plasmin and plasminogen) – streptokinase, urokinase**

	Functional Plasma Enzymes	Non-Functional Plasma Enzymes
Synthesis	by the liver	Intracellular enzymes <u>Different body organs</u> (Released by normal cell turnover)
Function	Perform specific functions in blood	No physiological function in blood
Substrates In blood	Present	Absent
Plasma levels	Higher than those in tissues	Very low under normal conditions They increase only in case of tissue damage; myocardial infarction ,hepatitis, cancer.
Examples	Enzymes of blood coagulation and fibrinolysis, Lipoprotein lipase,	Lactate dehydrogenase Creatinekinase Transaminases Alkaline phosphatase

Non functional plasma enzymes are present in higher concentration in cells compared to extracellular fluid

Increased activity of non functional plasma enzymes in extracellular fluid



Indicator of cellular damage

Unfortunately, there are few enzymes that are organ or tissue specific.

Examples:

Alcohol dehydrogenase in liver

Acid phosphatase in prostate

Pancreatic amylase and lipase

Isoenzymes

They are different molecular forms of the same enzyme synthesized by different tissues.

Same

Catalyze the same reaction

Act on the same substrate

Use the same coenzymes

Different

Subunits

V_{max} and K_m

Physical properties

Electrophoretic mobility,

Immunogenic properties

Heat stability

clinically important isoenzymes

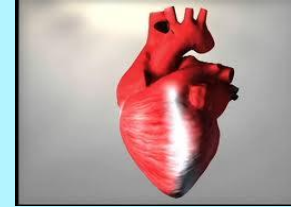
1-Lactate dehydrogenase

2-Creatinekinase.

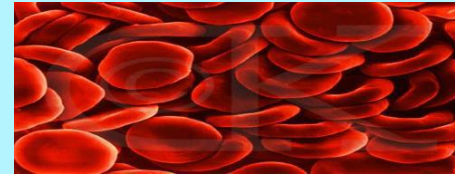
3-Alkaline phosphatase

Lactate dehydrogenase has Five isoenzymes present in blood

LDH1(HHHH) specific for HEART



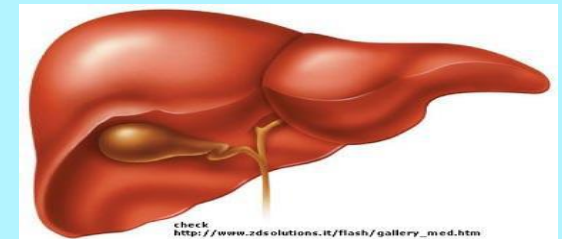
LDH2(HHHM) " " RBCs



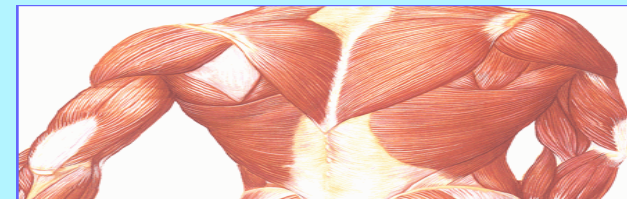
LDH3(HHMM) " " BRAIN



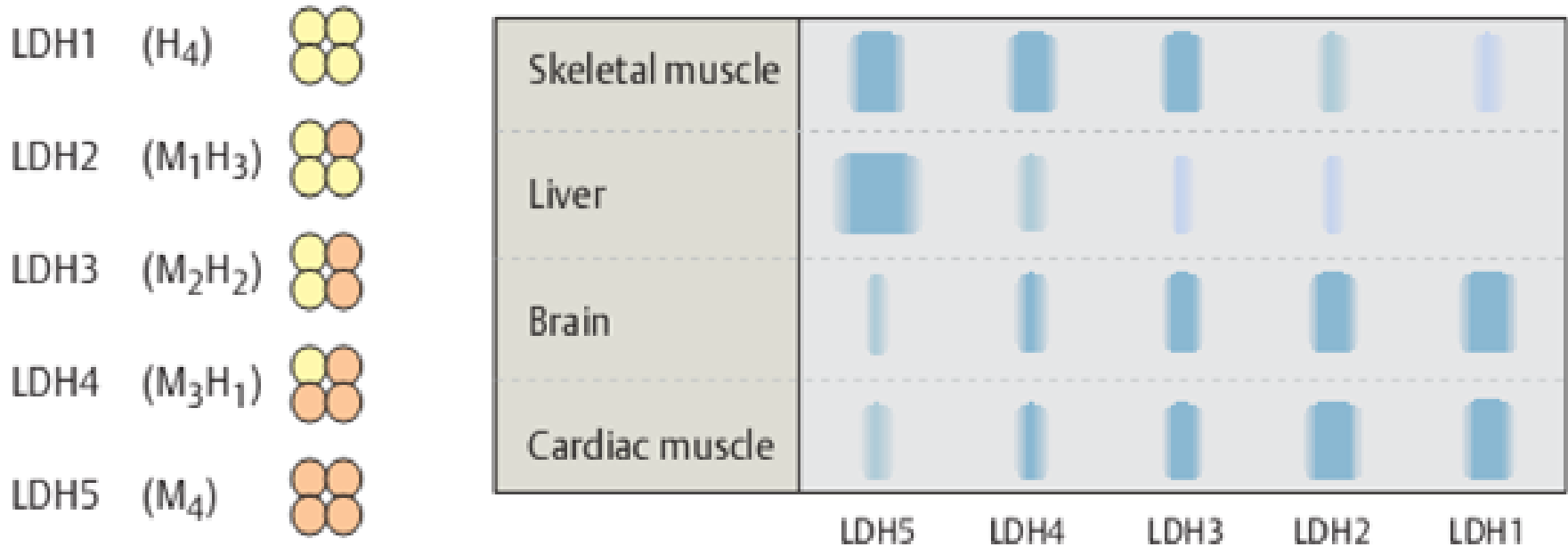
LDH4(HMMM) " " LIVER



LDH5(MMMM) " " MUSCLE



Electrophoresis of LDH



In myocardial infarction : Total serum LDH level increases due to elevation of LDH1 (cardiac) isozyme, electrophoresis is important to detect which fraction increased

Creatinekinase(CK)

Three isoforms are present

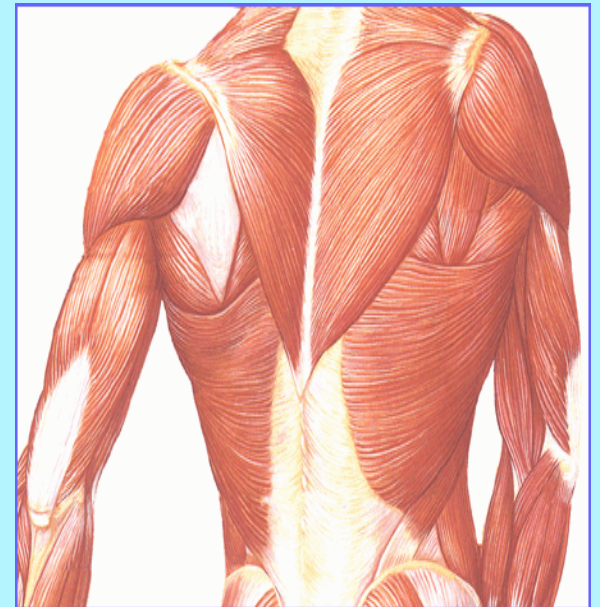
-CK 1 (BB) (Brain)

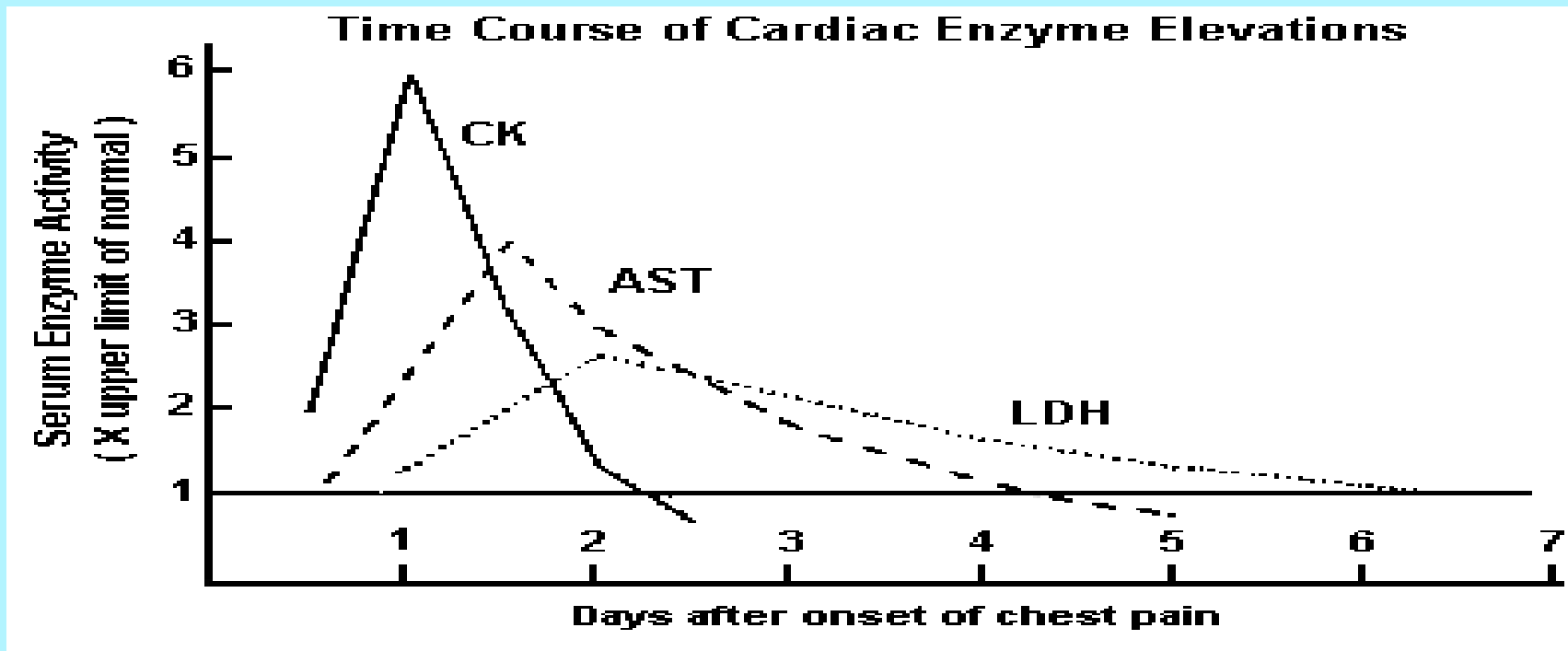
-CK2 (MB) (Heart)

-CK3 (MM) (Skeletal muscle)



In myocardial infarction there is elevation of total CK with marked elevation of CK2 (MB) after 4-8 hours
electrophoresis is important to detect which fraction increased





In myocardial infarction, the cardiac isoenzymes of both CK&LDH are increased , **CK2 rises within 4-8 hours after the onset of pain reaches peak within 24 hours**. It returns to normal level after two-three days. LDH1 reaches its peak after **36-40 hours** returns to normal level after 48 hours

Alkaline phosphatase

isoenzymes present in blood, are derived from bone, liver, intestine or placenta of pregnant woman

Electrophoretic separation of isoenzymes(different numbers of sialic acid residues) is performed to determine the organ affected.

Increased ALP

Normal elevation

Pregnant women
Growing children
Adolescent

Moderate increase

Liver disease e.g.
hepatitis
,obstructive
jaundice

Very high level

Bone disease e.g.
ricket,
osteomalacia and
cancer

Some enzymes are used as Therapeutic agents

Streptokinase:

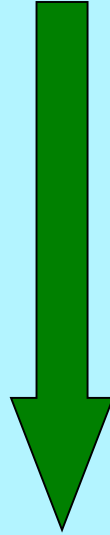
Enzyme prepared
from
streptococcus

Used in clearing
blood clots in
**myocardial
infarction**

Act by activating
*plasminogen to
form plasmin.*

Plasmin cleaves
fibrin into several
soluble
components

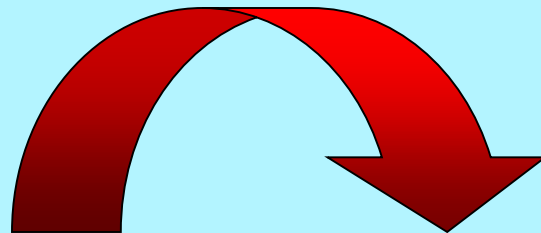
Plasminogen



Sterptokinase

Plasmin

Fibrin



FDP

Asparaginase: enzyme used in therapy of adult *leukemia* ,

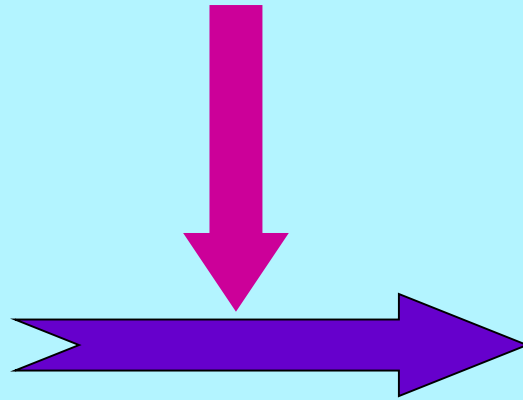
Tumor cells
have
nutritional
requirement
for
asparagine,

Asparaginase
is
administrated
decreasing
asparagine
level

Asparaginase
depresses
the viability
of tumor

Asparaginase

Asparagine



Aspartic acid

Asparagine is required as nutrition for tumorcells

Asparaginase used in treatment of Leukaemia

Use of **asparaginase** will decrease asparagine level so inhibiting tumor growth (depress the tumor vitality)

THANK YOU