r"

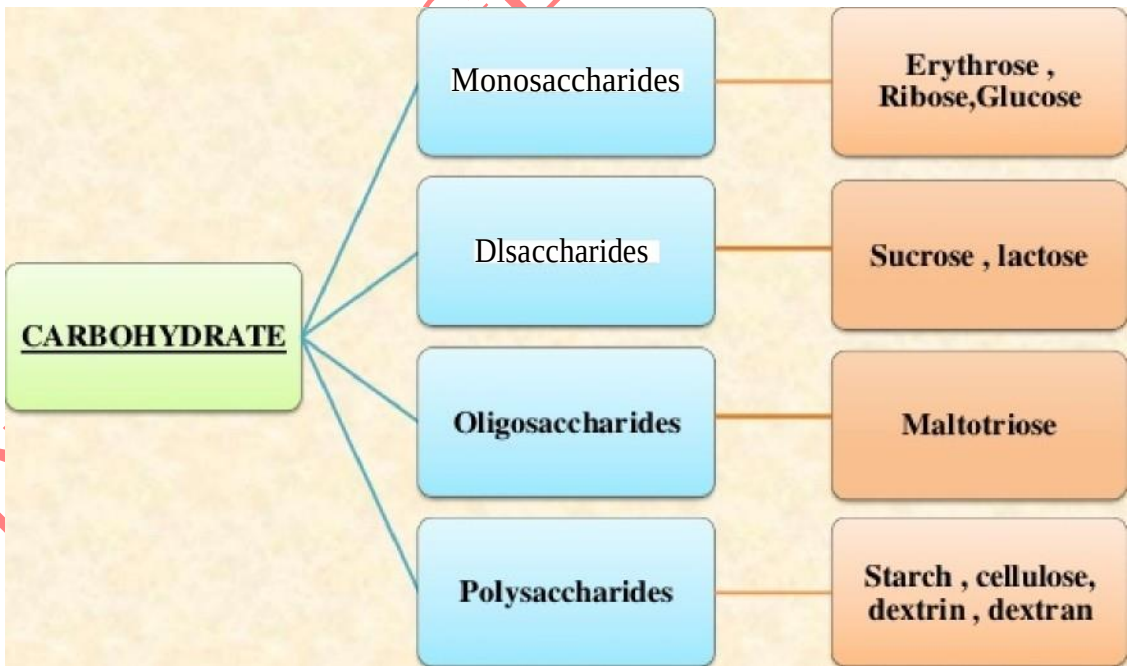
CARBOHYDRATE:

V Most abundant organic molecule on earth.

N Corbohydrates are defined as aldehyde or keto derivatives ofpol 'hydric alcohoLv.

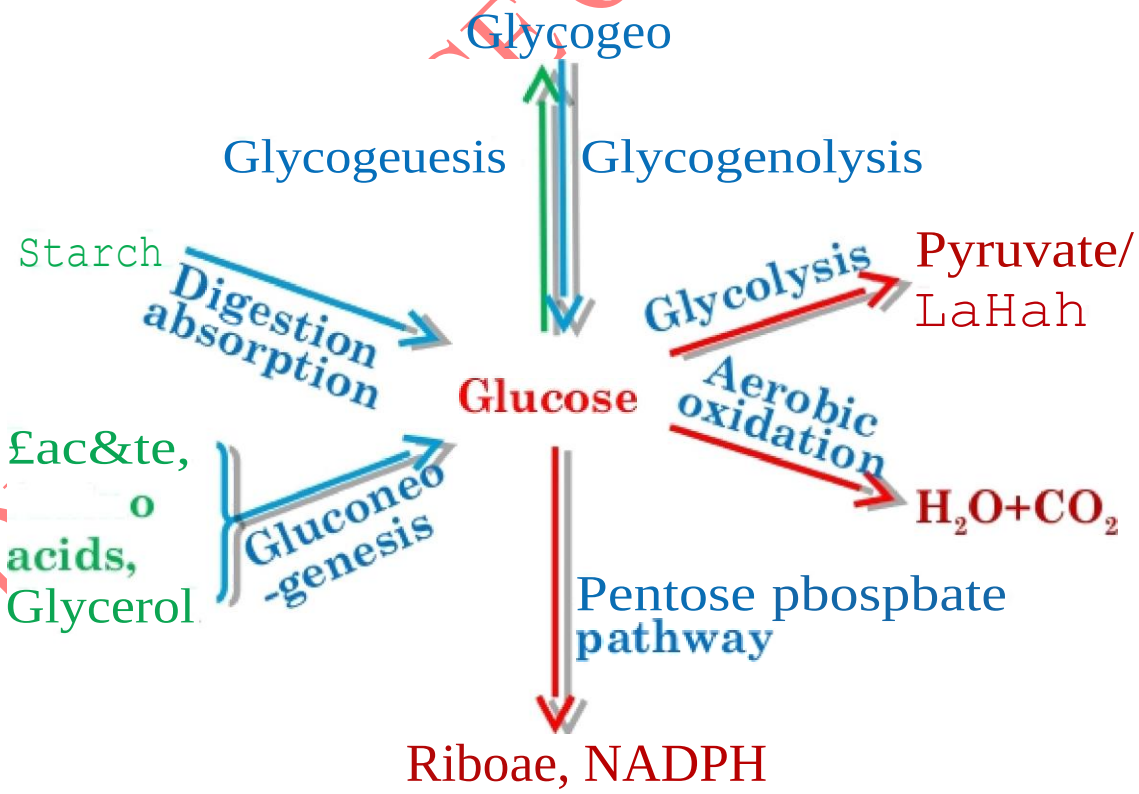
V Fc›r example: Glycerc›l on c›xidatic›n is converted tn D-glyceraldehyde, which is a carbc›hydrate derived from the trihydric a1cc›hol (glycerc›l).

V All carbohydrates have the general formula C HJ,O, [orit can be re- written as C (HCO)]



The metabolism of glucose

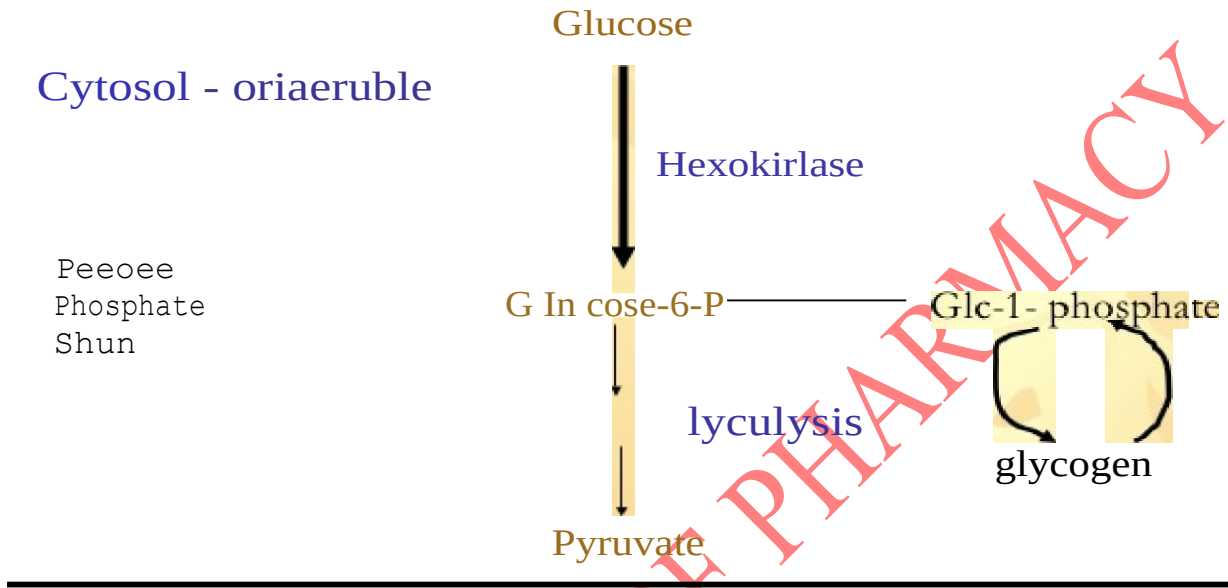
- Aerobic oxidation
- Glycolysis
- Gluconeogenesis
- Pentose phosphate pathway
- Glycogenesis
- Glycogenolysis
- Uronic acid pathway

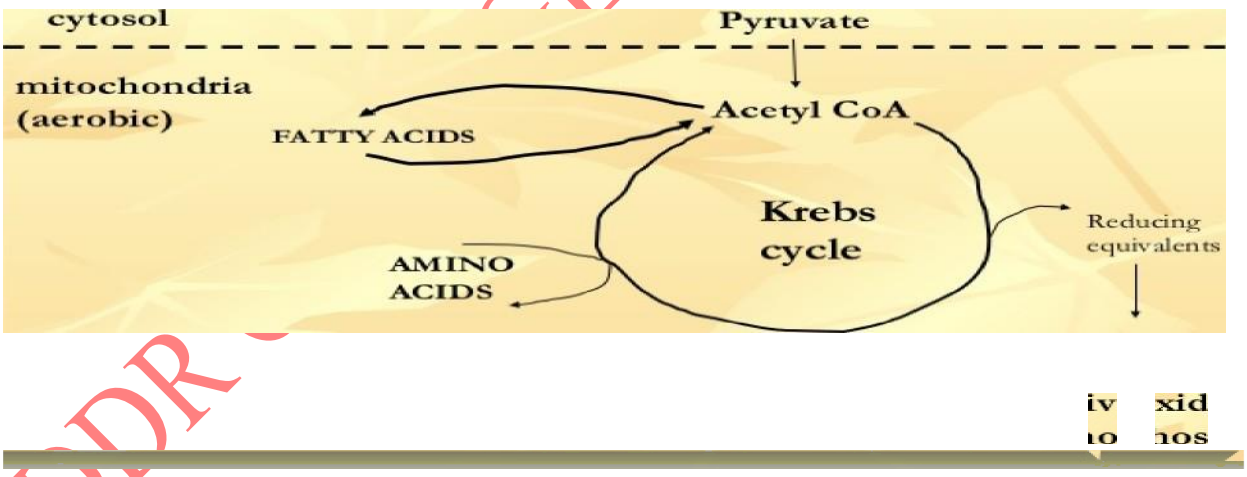


MAJOR PATHWAYS OF CARBOHYDRATE METABOLISM

Carbohydrates

- Serve as primary sowce of energy in the cell
- Centml to all metabolic processes





Glycolysis

Defn: It is defined as sequence of reactions of glucose to lactate & pyruvate with the production of ATP.

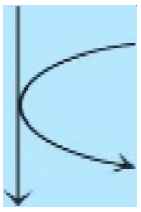
It is derived from greek word *glycose* -sweet or sugar, *lysis*- dissolution.

Site: Cytosolic fraction of cell

GL¥C0L¥SIS

STAG£I

Hexokinase



ATP

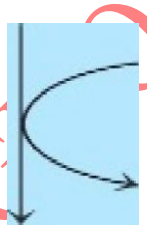
ADP

cl ucose-6 - phosphate

Phosphoglucose isorrierase

Fructase-6-phosphate

Ph ospho-fructokinase

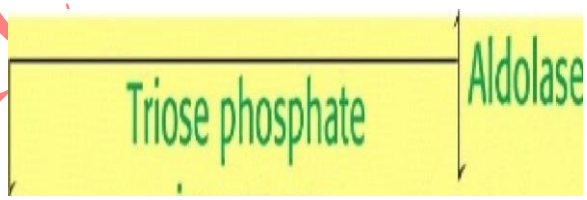


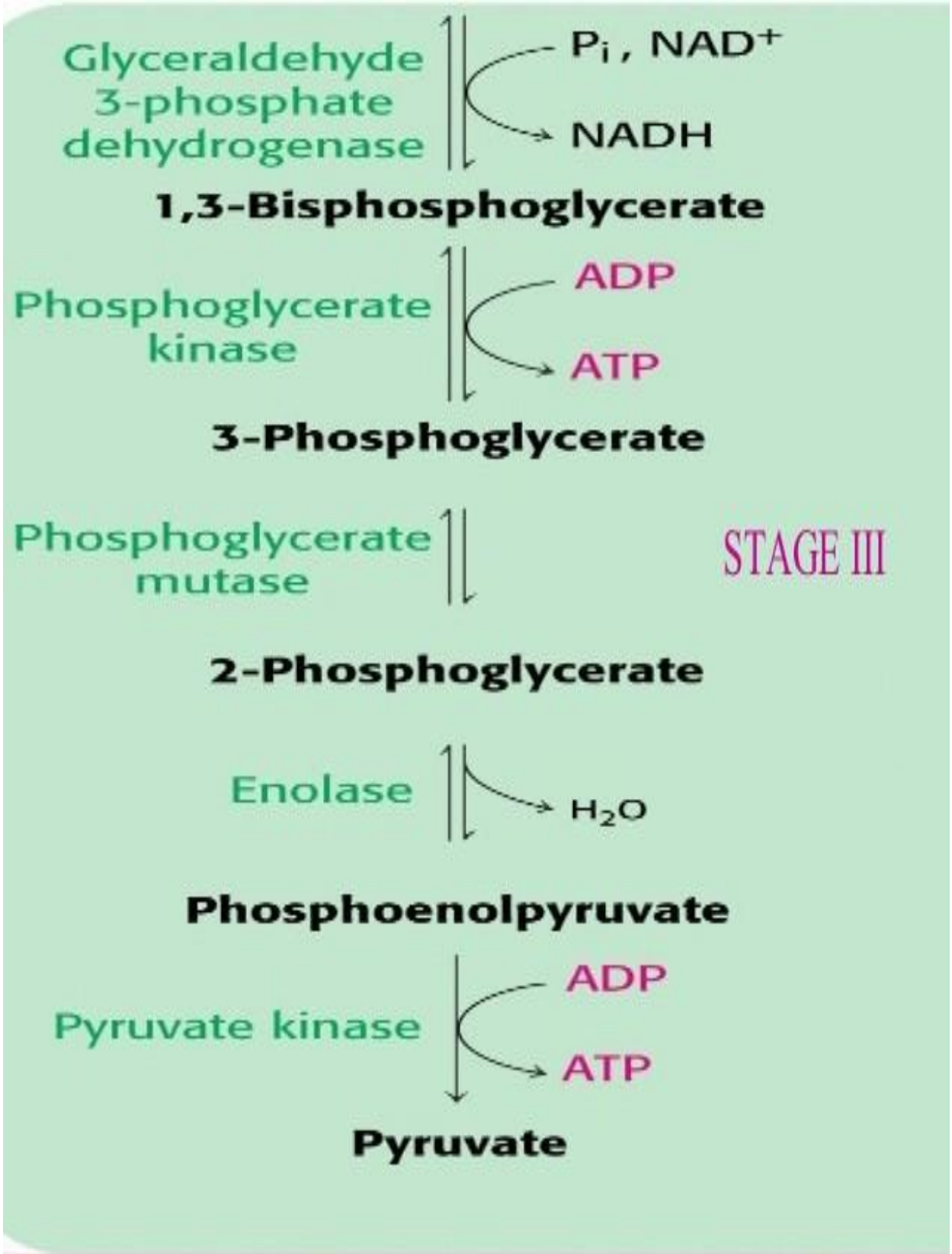
ATP

ADP

Fructose-1,6-bisphosphate

STAGE II




Glyceraldehyde 3-phosphate dehydrogenase
Pi , NAD+
NADH
1,3-Bisphosphoglycerate
Phosphoglycerate kinase
ADP
ATP
3-Phosphoglycerate
Phosphoglycerate mutase
STAGE III
2-Phosphoglycerate
Enolase
H2O
Phosphoenolpyruvate
Pyruvate kinase
ADP
ATP
Pyruvate

Bioenergetics in Glycolysis:

Total of 8 ATP is fomed in glycolysis.

Oxidation of glucose in aerobic condition:38 ATP

Anaerobic condition: 2 ATP

Biomedical importance of Glycolysis

- Principal route of metabolism,
- Production of acetyl coA in citric acid cycle.
- Metabolism of fructose & galactose.
- Provides ATP in absence of Oxygen,

Metabolism of Glycogen

" Major storage form of carbohydrate,

" Glycogenesis: occws in muscle & liver,

Reactions of Glycolysis

1) Energy Investment phase priming phase

2) Splitingphase

3) Energygenerationphase

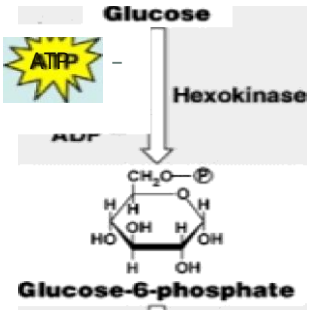
- **Glucose** is phosphorylated to **glucose-6-phosphate** by *hexokinase (or) glucokinase.*
- Glucose-6-phosphate undergoes isomerization to give **fructose -6- phosphate** in the presense of
- Fructose-6-phosphate is phoshorylated to **fructose 1,6-bisphosphate** by *phosphofructokinase.*

Splitting

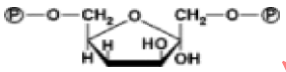
- Fructose 1,6-bisphosphate → **glyceraldehyde 3-phosphate + dihydroxyacetone phosphate.**(*aldolase enzyme*)

2 molecules of glyceraldehyde 3-phosphate are obtained from 1 molecule of glucose

- Glyceraldehyde 3-phosphate → **1,3-bisphosphoglycerate**(*glyceraldehyde 3-phosphate hydrogenase*)
- 1,3-bisphosphoglycerate → **3-phosphoglycerate** (*phosphoglycerate kinase*)
- 3-phosphoglycerate → **2-phosphoglycerate** (*phosphoglycerate mutase*)
- 2-phosphoglycerate → **phosphoenol pyruvate** (*enolase* + Mg^{2+} & Mn^{2+})
- I'li‹›h[›li‹Kii‹›l[›}i"uxale4 pt"rutaJe l+nM i / \ ir\rr r‹' fi r irr.›‹' i4 pt rutaJe [keh]4 I.•tac1ale

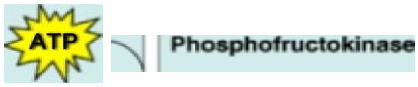


Phoaghoglucoiaomeraae



1, 6-bisphosphate

t Aldolase



ADP "

I I

z ao" -- Trioae phosphate dehydrogenase

— O—C 0

CHOH

EHR — O —''

1, 3-Bisphosphoglycerate

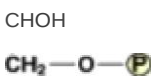
2 AOP

z,

ATR "

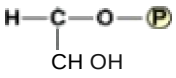
Phosphoglycerokinase

CHOH



Pheophoglyceromutaaa

C—0



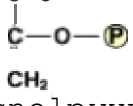
CH OH

Enolase

2 „

2 0·

C—O



CH_2

oephocnolpyxvate

2 ADP

Pyruvate kinase

2 0

C—O

C—O

CH_3

Pyruvate

3. Significance of glycolysis

1) Glycolysis is the emergency energy-yielding pathway.

2) Glycolysis is the main way to produce ATP in some tissues, even though the oxygen supply is sufficient, such as red blood cells, retina, testis, skin, medulla of kidney.

- In glycolysis, 1mol G produces 2mol tactic acid and 2mol ATP.

CITRIC ACID CYCLE

KREBS CYCLE / TRICARBOXYLIC ACID/ TCA CYCLE

Essentially involves the oxidation of acetyl CoA to CO_2 and H_2O.
This Cycle utilizes about two-third of total oxygen consumed by the body.

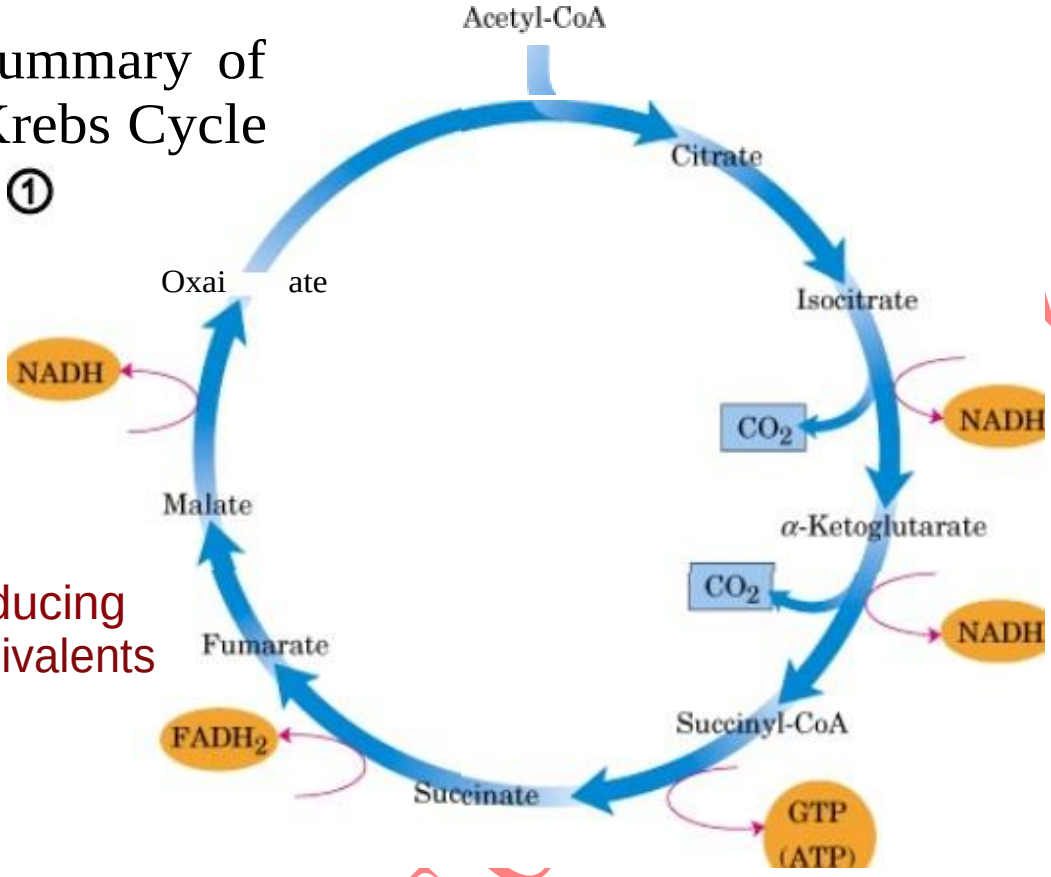
2) Tricarboxylic acid cycle, TCAC

- The cycle comprises the combination of a molecule of acetyl-CoA with oxaloacetate, resulting in the formation of a six-carbon tricarboxylic acid, citrate. There follows a series of reactions in the course of which two molecules of COC are released and oxaloacetate is regenerated.
- Also called citrate cycle or Krebs cycle.

Brief History:	Location of TCA	Overview
• Hans Adolf Krebs • 1937 • Studies of oxygen consumptiom in pigeon breast muscle.	• Mitochondrial matrix • In close proximity to the electronic transport chain.	• 65-70% of the ATP is synthesized • Name : TCA used because at the ouset of the cycle tricarboxylic acids participate.

Summary of Krebs Cycle

①



Reducing equivalents

Reactions of citric acid cycle

1) Formation of citrate : Condensation of acetyl CoA and oxaloacetate G catalysed by citrate synthase.

2) & 3) Citrate is isomerized to isocitrate G aconitase (two steps).

4) & 5) Formation of -ketoglutarate : enzyme isocitrate dehydrogenase.

6) Conversion of -ketoglutarate to succinyl CoA : through oxidative decarboxylation, catalysed by O-ketoglutarate dehydrogenase complex.

7) Formation of succinate : enzyme succinate thiokinase

GTP + ADP T-G ATP + GDP (nucleoside diphosphate kinase)

8) Conversion of succinate to fumarase : enzyme succinate dehydrogenase

9) Formation of malate : enzyme fumarase

10) Conversion of malate to oxaloacetate : enzyme malate dehydrogenase.

- TCA cycle is strictly **aerobic** in contrast to glycolysis.

- Total of 12 ATP are produced from one acetyl CoA :-

  During the process of oxidation of acetyl CoA via citric acid cycle W 3 NADH & 1FADH2.

  Oxidation of 3 NADH by electron transport chain coupled with oxidative phosphorylation results in 9 ATP, FADH2 G 2 ATP.

  One substrate level phosphorylation.

(2) Bio-significance of TCAC

O Acts as the final common pathway for the oxidation of carbohydrates, lipids, and proteins.

@ Serves as the crossroad for the interconversion among carbohydrates, lipids, and non-essential amino acids, and as a source of biosynthetic intermediates.

Biomedical importance

- Final common pathway for oxidation of cubohydrates, lipids , & proteins.
- Major role in gluconeogenesis, transamination, dearnination & lipogenesis.
- Vitamins play a key role in this cycle

  Eg; Riboflavin — FAD.

  Niacin — NAD.

  Thiamine.

  Pantothenic acid as a part ofco-A.

Bioenergetics :12 ATP per cycle.

HEXOSE MONOPHOSPHATE SHUNT

HhlP Shunt/ Pentose Phosphate Pathway/ Phosphogluconate Pathway

* This is an alternative pathway to glycolysis and TCA cycle for the oxidation of glucose.

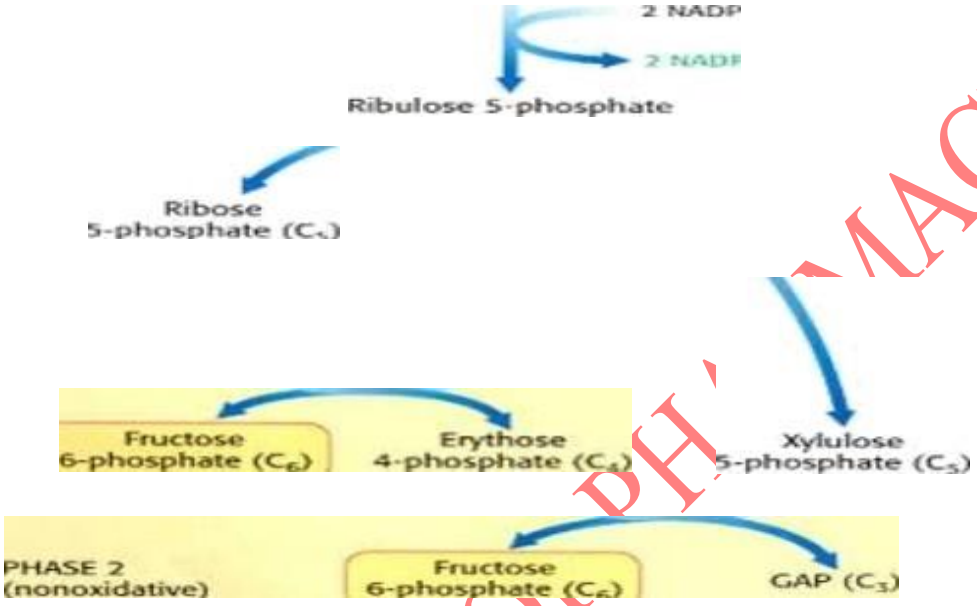
* Anabolic in nature, since it is concerned with the biosynthesis of NADPH and pentoses.

* Unique multifunctional pathway

* Enzymes located – cytosol

* Tissues active – liver, adipose tissue, adrenal gland, erythrocytes, testes and lactating mammary gland.

Reactions of the HMP Shunt Pathway



Significance of HMP Shunt

- Pentose or its derivatives are useful for the synthesis of nucleic acids and nucleotides.

- NADPH is required :
  - For reductive biosynthesis of fatty acids and steroids.
  - For the synthesis of certain amino acids.
  - Anti-oxidant reaction
  - Hydroxylation reaction— detoxification of drugs.
  - Phagocytosis
  - Preserve the integrity of RBC membrane.

Clinical Aspects

- Glucose-6-Phosphate dehydrogenase deficiency
  - Inherited sex-linked trait
  - Red blood cells
  - Impaired synthesis of NADPH
  - hemolysis , developing hemolytic anemia

  Resistance towards malaria [Africans]

Clinical Aspects

- Wernicke-Korsakoff syndrome :
  - Genetic disorder
  - Alteration in wansketolase activity
  - Symptoms : mental disorder, loss of memory, partial paralysis

- Pernicious anemia : transketolase activity increases.

Von-Gierke's disease

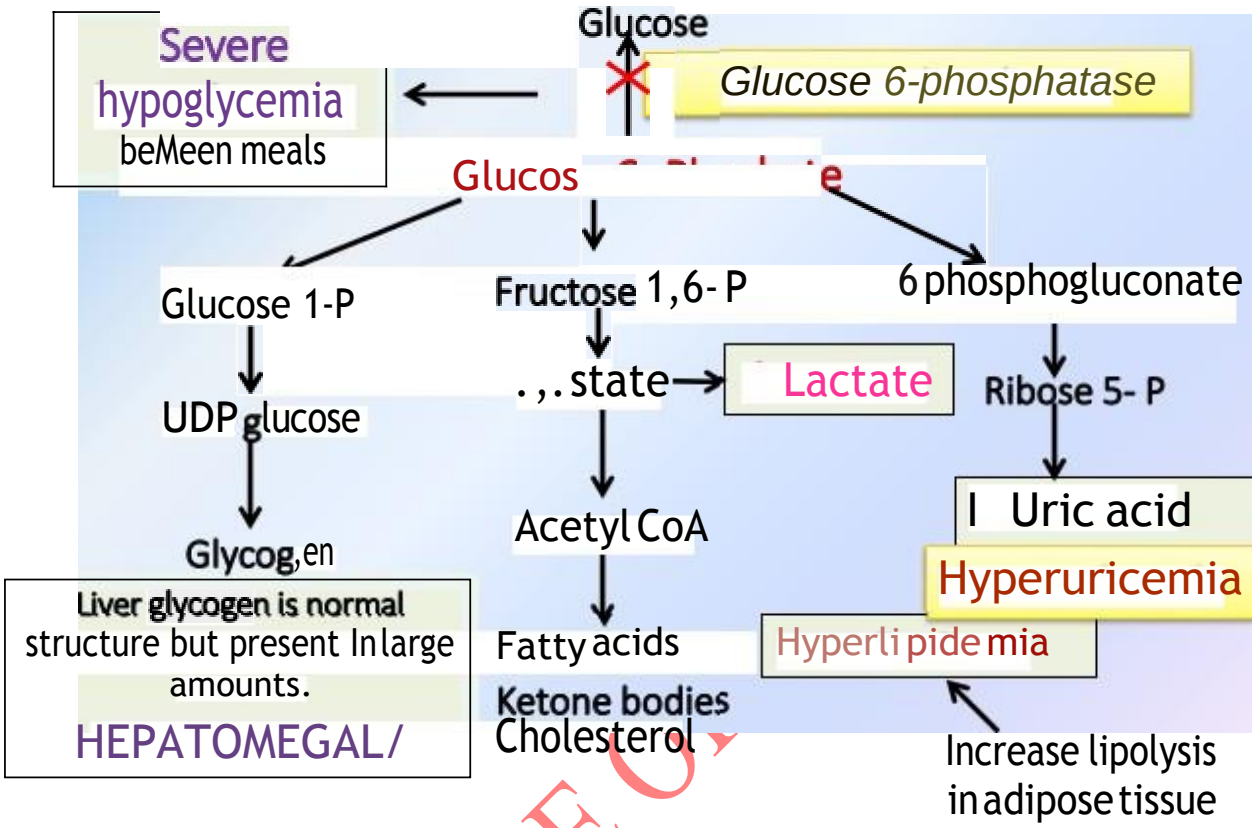
Affected enzyme: Glucose 6 phosphatase deficiency

Affected tissue: Liver and kidney

Clinical features:

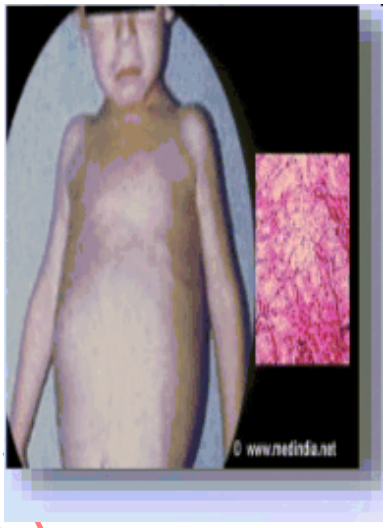
- Hypoglycemia
- Lactic acidosis
- Hepatomegaly – progressing to cirrhosis
- Hyperuricemia
- Hyperlipidemia

Type I (VonGierke's disease)



Sym †OffIS •

- Enlarged Liver And Kidneys
- Low Blood Sugar
- High Levels Of Lactate, Fats, And Uric Acid In The Blood
- Impaired Growth And Delayed Puberty
- Bone Thinning From Osteoporosis
- Increased Mouth Ulcers And Infection



Diagnosis - by Liver Biopsy .

Treatment – by frequent meals , nasogastric feeding at night to maintain blood glucose concentration.

GLUCONEOGENESIS

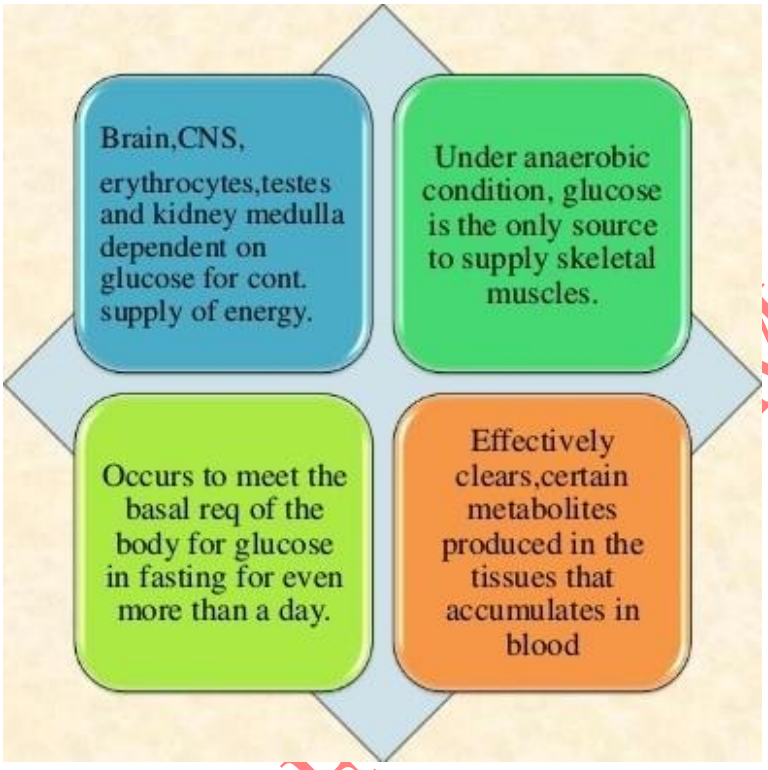
The synthesis of glucose from non-carbohydrate compounds is known as gluconeogenesis.

Major substrate/precursors : lactate, pyruvate, glycogenic amino acids, propionate & glycerol.

-Takes place in liver (1kg glucose) ; kidney matrix(1/3rd).

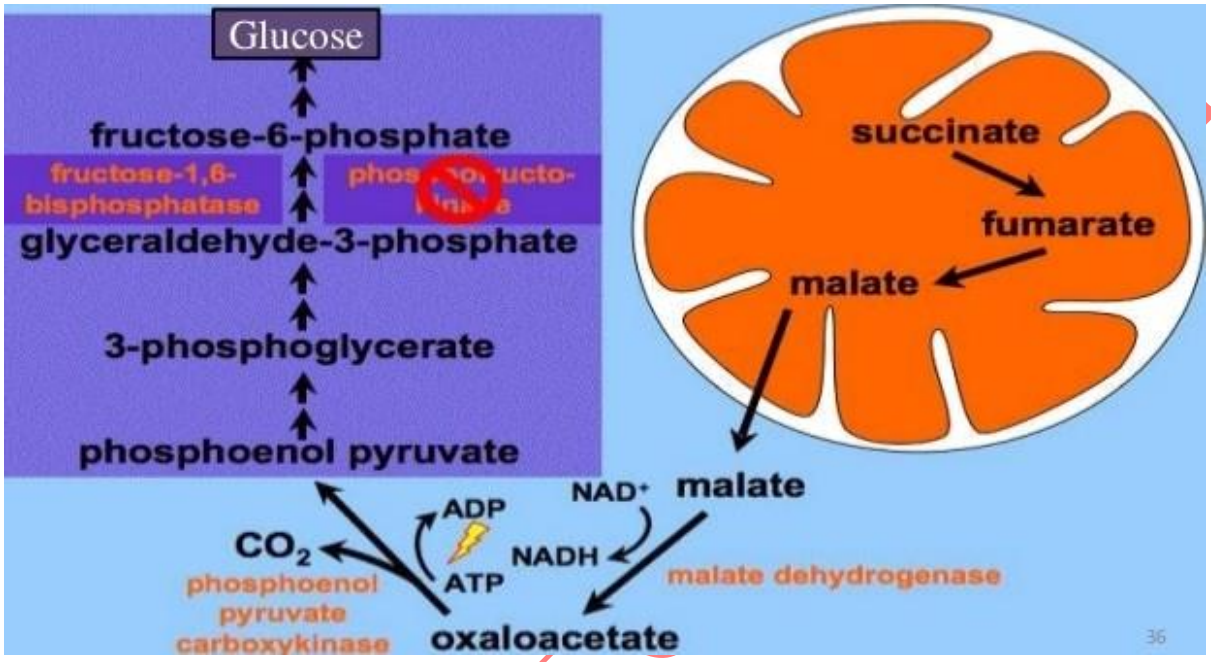
- Occurs in cytosol and some produced in mitochondria.

Importance of Gtuconeogenesis



Reaction of Gluconeogenesis

OluconeogenesT6t Running Olyeolyais In Reverse



3. Significance of gluconeogenesis

(1) Replenishment of Glucose by Gluconeogenesis and Maintaining Normal Blood Sugar Level.

(2) Replenishment of Liver Glycogen.

(3) Regulation of Acid-base Balance.

QLYCWER

METABOLISM

Glycogen is n storage form of glucose in animals.

Staied mostly in liver (d-BE) and muscle (1-2%)

<Due to muscle mass the quantity of glyoogen in muscie = 250g
nut liver =75g

<Stored us granules in the cytosol.

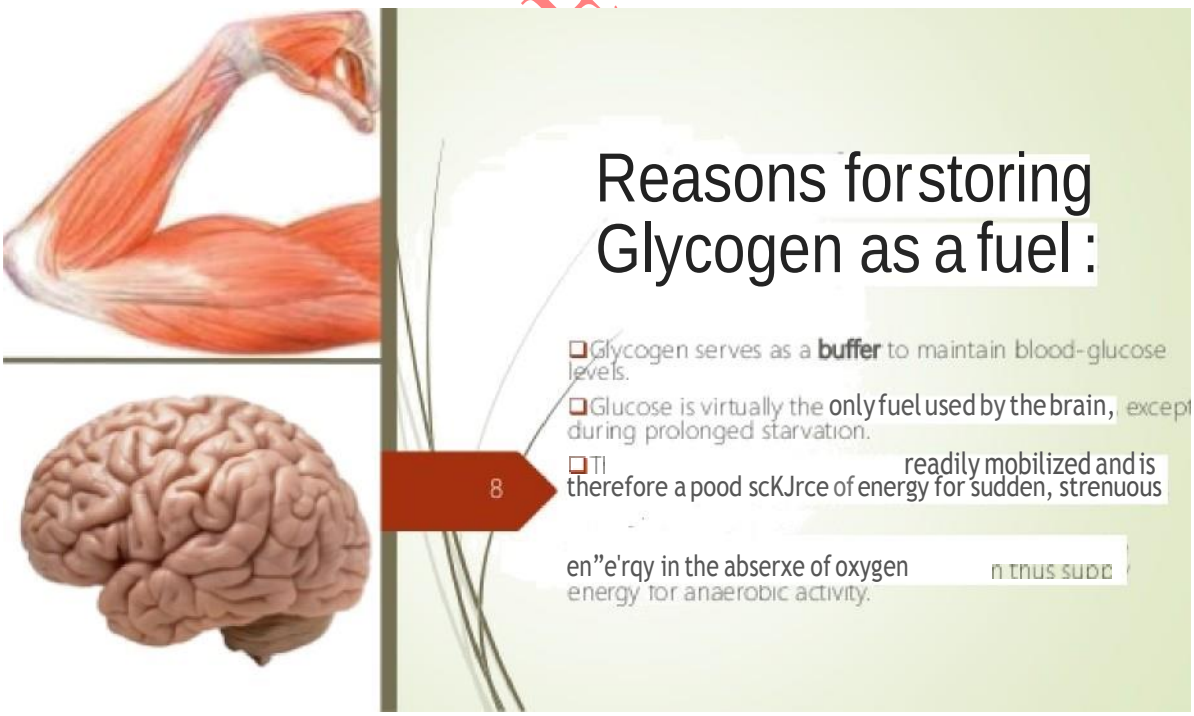
Funcbons : Liver glycogen — maintain the blood glucose level
Muscle glycogen — serves as fuel reserve

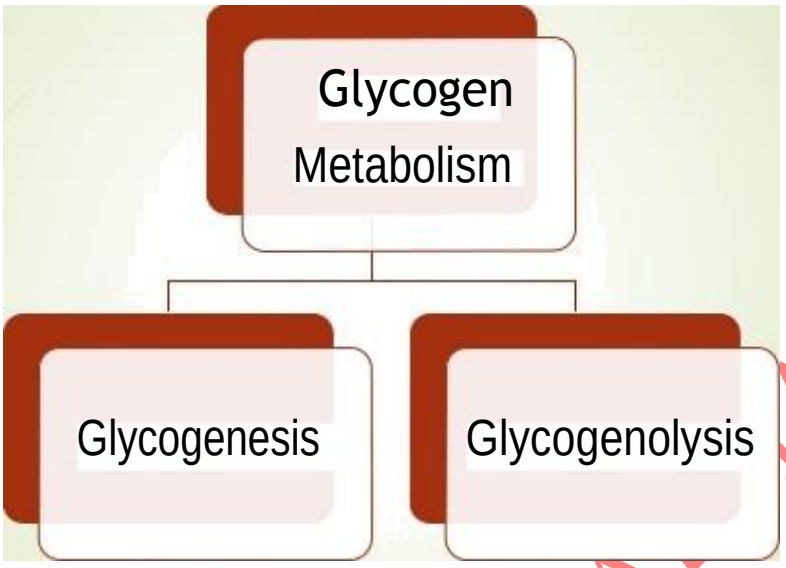
Liver glycogen maintain blood glucose level particularly between meals.

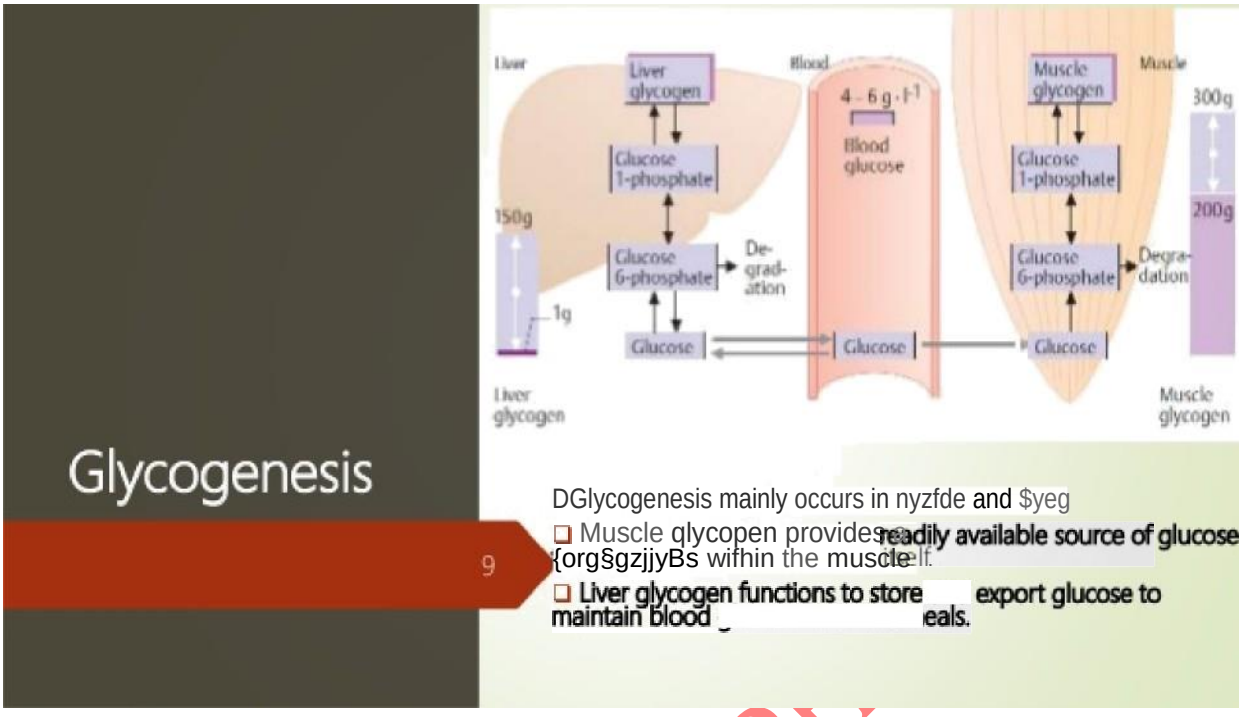
First line of defense against declining blood glucose levels especially between meals.

Muscle glycogen is a readily available source of glucose in the exercising muscles.

Deficient mobilization and abnormal accumulation of glycogen leads to certain disorders called as GLYCOGEN STORAGE DISEASES which can lead to muscular weakness and even death in the affected individual.







Glycogenesis is the process of **Glycogen synthesis**

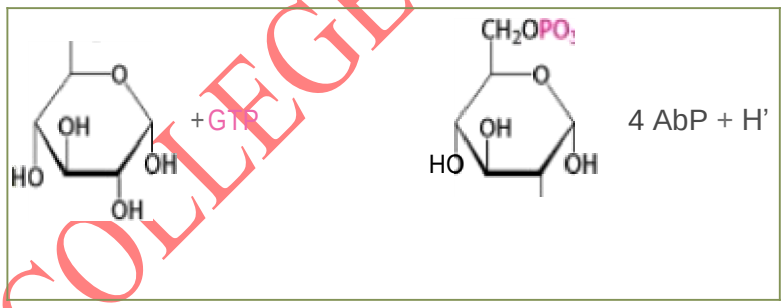
- Glycogen is synthesized when blood glucose levels are high .
- Glucose is converted into glucose-b-phosphate by the action of:
  Hexokinase catalyses this reaction in most tissues.
  In the liver and pancreas there is an extra enzyme; Glucokinase exhibiting different kinetic properties.

Phases of Glycogenesis

12

Activation | Initiation | Elongatio | Glycogen Branching

Step-1- Phosphorylation of Glucose



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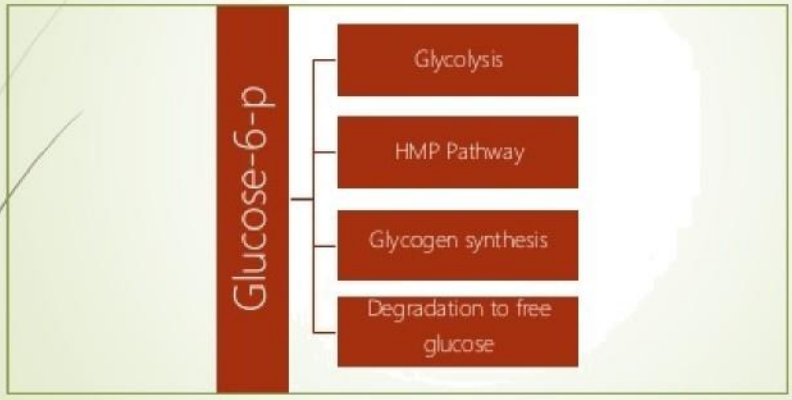
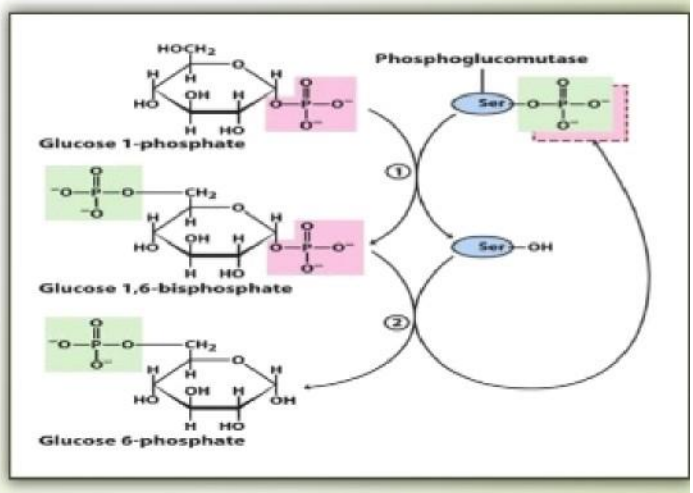
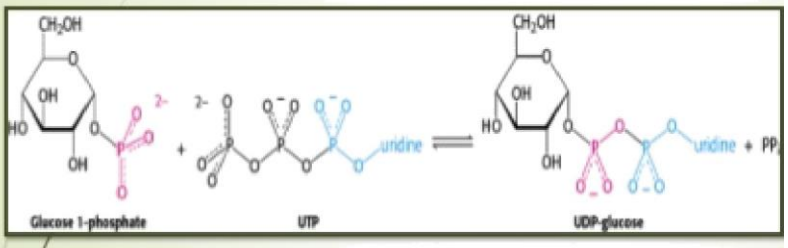
Fate of Glucose-6-P



Step-2- Convenion of Glucose-6-P to Glucose-1-P



Step-3- Conversion of Gluco5e-1-P to UDP-Glucose



Synthesis of UDP-6lucoe : Activated form of 6lucose

Glucose

AYP

ADP

Glucokinase
Hexokinase

Glucose-6-phosphate

ewures †he Irreversibilify of †his reaction.

Phosphoglucomutase

Glucose-l-phosphnte

UYP

PPi

Pyrophosphatase

2Pi

U bP - Glucose pyrophosphorylnse

UDP- Glucose

SynthesiS «•f Primer

to initiate Glycogen synthesis:

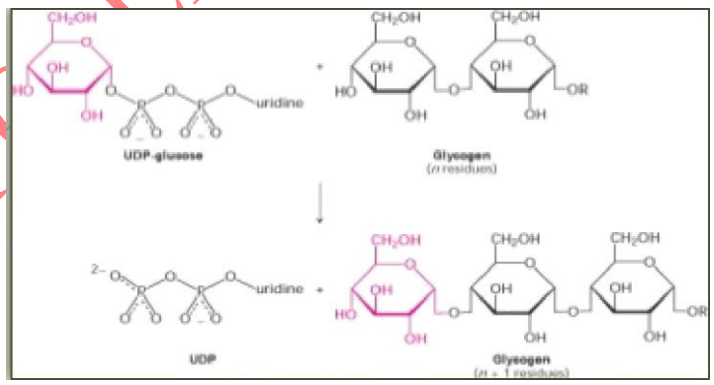
Primer is a preexisting a (144) glucosyl chain which will accept the

glucosyl residues donated by UDPG.

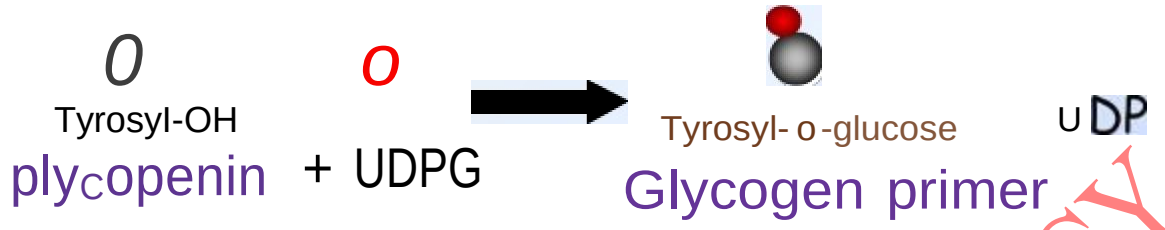
- " Normally a fragment of glycogen serves as a primer.
- '^ When glycogen stores are depleted, a specific protein known as

GLYCOGENIN provides the site at which the primer is built.

Incorporation of UDP-Glucose into-qlycogen

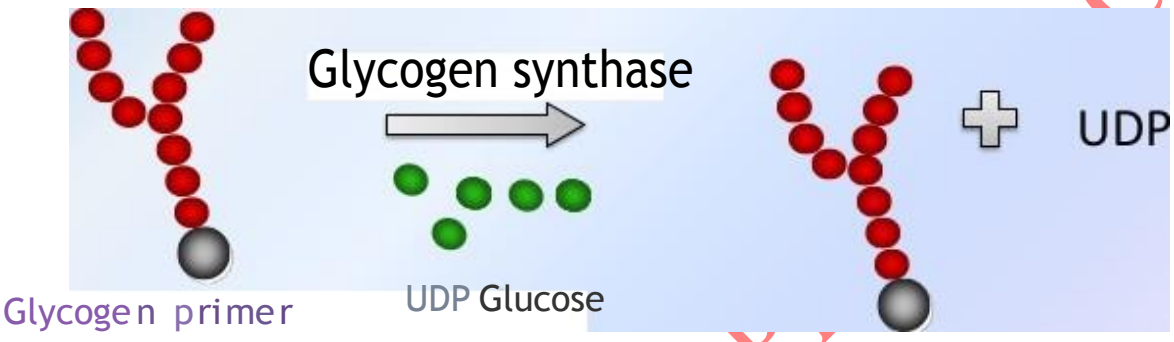


UDP + ATP ⟶ UTP + ADP



Elongation of the chain:

6lycogen Synthase - Key Regulatory Enzyme in 6lycogen Synthesis



Formation of Branches in Glycogen:

The branch point - created by the action of Branching enzyme or glucosyl 4:6 transferase.

When the chain is minimum 11 glucose residues long, branching enzyme removes a block of 6-8 glucosyl units from the non reducing end of the chain and attaches it via an a(1—+6) linkage to a glucose residue of the same or other chain.

Lysosomal degradation of Glycogen

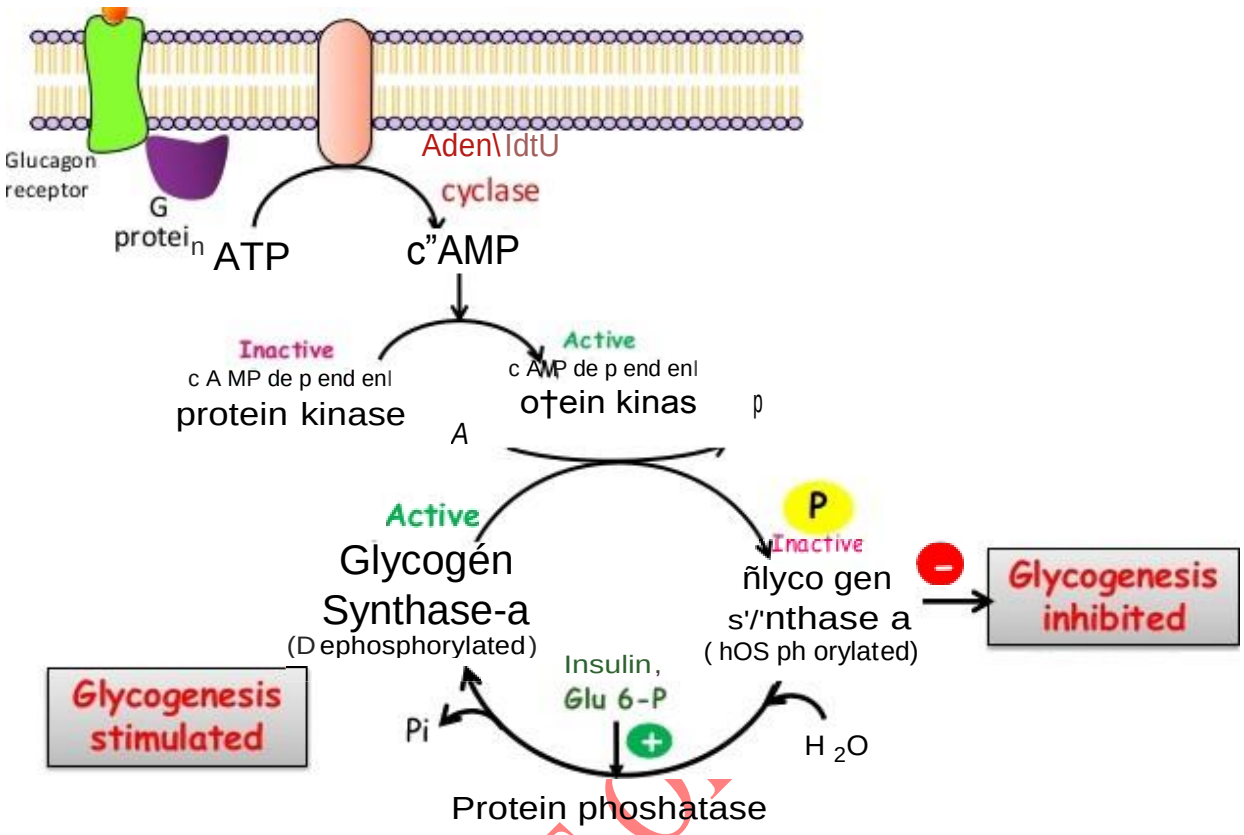
@ A SITtQ QITtOUf\† OF '/'CO ‹2f\ iS COf\†if\UOUS '/' degraded in the lysosomes.

By †he lysosomal enzyme a-1,4-glucosidase (acid maltese).

GB The significance of †his pathway is unknown. However, a deficiency of this enzyme cause accumulation of glycogen in the cytosol.

Results in glycogen storage disease type II (Pompe's disease)

GI ucagon



Glycogen Degradation (Glycogenolysis)

Definition: It is the degradation of glycogen to glucose 6-phosphate & glucose in muscle & liver respectively.

Substrate: Glycogen

Si†e: Liver, Skeletal Muscles

Subcellulor si†e: Cytosol.

Steps: 1.Action of Glycogen Phosphorylase

2.Action of Debronching Enzyme

3.Formation of Glucose.

Action Of Glycogen Phosphorylase

1.The Key enzyme of glycogenolysis — Glycogen Phosphorylose.

Phopshorolytic cleavage of a(1) glycosidic bonds to form limit Dcxtrin.

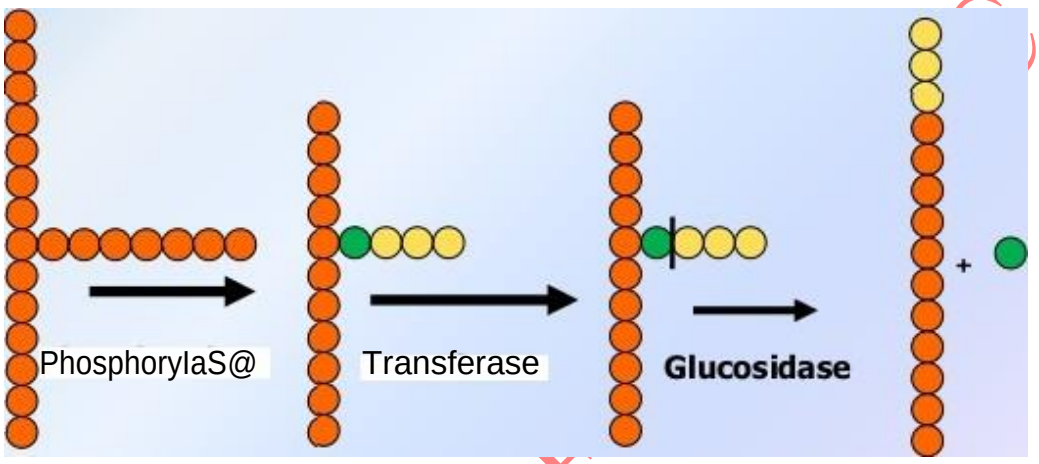
Debranching Enzyme – Bifunctional

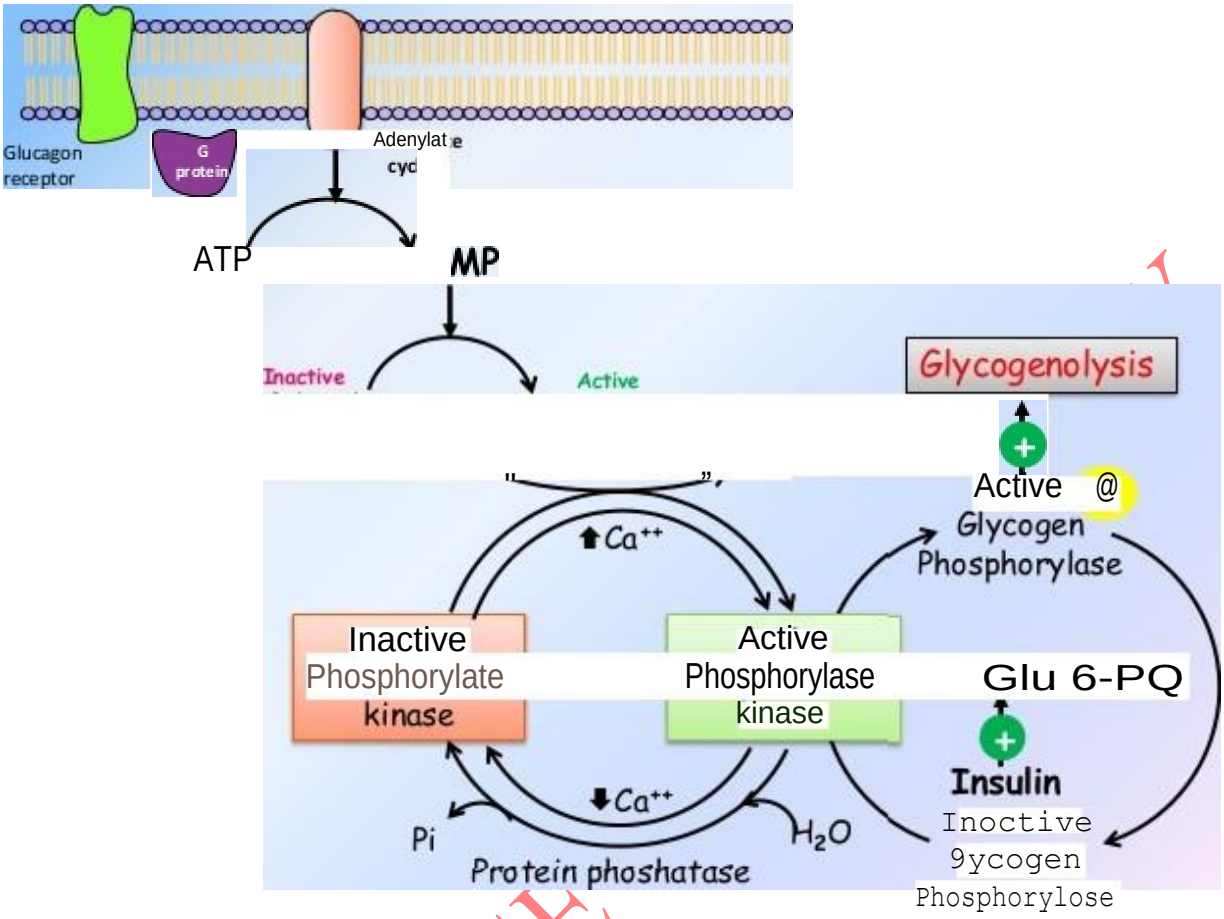
Glucosyl 4:4 transferase activity transfers the 3 of the 4 glucosyl units and involves cleaving of an a(1E4)linkage at one site and formation of new a(1E4)bond elsewhere.

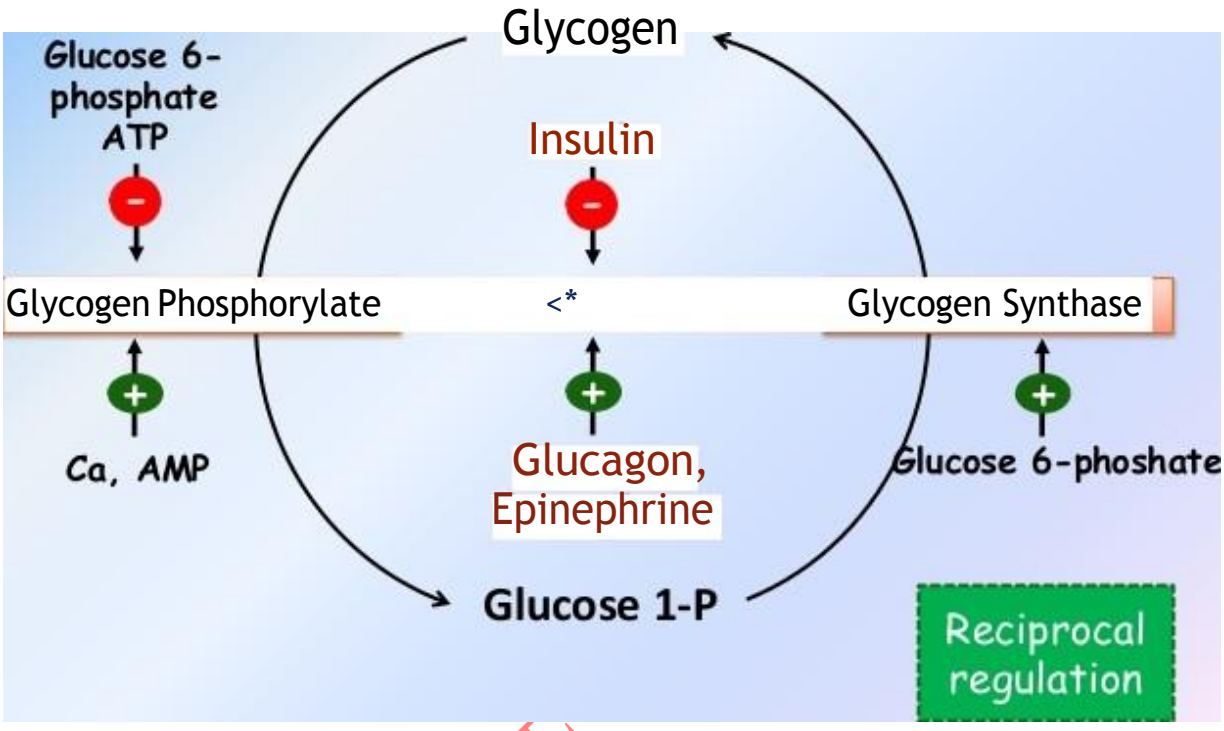
The key enzyme for removing branch points is the debranching enzyme - a (1G6) glucosidase — breaks a (1E6) bonds - free glucose released.

Ratio of Glu-1-P to Free Glucose — 8:1.

Glycogenolysis:




Glucagon receptor
G protein
Adenylat e
cyc
ATP
MP
Inactive
Active
Glycogenolysis
Active @
Glycogen
Phosphorylase
Ca++
Inactive
Phosphorylate
kinase
Active
Phosphorylase
kinase
Glu 6-PQ
Insulin
Inoctive
9ycogen
Phosphorylose
Ca++
Pi
H2O
Protein phoshatase


Glycogen
Glucose 6-phosphate ATP
Insulin
Glycogen Phosphorylate
<*
Glycogen Synthase
Ca, AMP
Glucagon, Epinephrine
Glucose 6-phoshate
Glucose 1-P
Reciprocal regulation

Glycogen Metabolism(Summary)

oGlycogen re presen ts the **principal** storage form of carbohydrate in the body, mainly in the liver and mu

oGlycogen is synthesized from glucose by the pathway of glycogenesis.

oIt is broken down by a separate pathway, glycogenolysis. Glycogenolysis leads to g lucose formation in liver and lactate formation in muscle owing to the respective presence or absence of glucose 6— phos phatase.

uCyclic AMP integrates the regulation **of glycogenolysis** and glycogenesis by promoting the simultaneous activation of ph as phorylase and i nhibition of glycogen syntha5e.

- **Insulin acts reciprocally by inhibiting glycogenolysis and stimulating glycogenesis.**
- Inherited deficiencies in s pecific en z mes of glycogen metabolism in both liver and muscle are the causes of glycogen storage diseases.

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Biological significance

When the blood glucose b low as in fasting or starvation, the predominant hormones such as Glucagon and epinephrine trigger the E- AMP mediated phosphorylation cascade.

LJIn the phosphorylated state glycogen synth ase becomes inactive whereas Phosphorylase becomes active,

I JGlycogenesis is switched "off" and Glycogenolysis is switched "on".

LJLiver glycogen breakdown restores the lowered blood glucose concentration back to normal

Biological significance

When the blood glucase concentration 1s hlgh- Insulin, the main hormone, promotes the dephosphorylated forms of the enzymes by disrupting the c AMP mediated phosphorylation cascade and by stimulating the phosphatase activ"/ties.

GPhosphorylase in the dephosphorylated form becomes inactive whereas the Glycogen synthase in that state becomes active.

OHence extra glucose is used for glycogen synthesis and blood glucose concentration is restored back to normal.

Conclusion

OGlycogenesis and glycogenolysis are reciprocally regulated.

Olnsulin promotes glycogenesis.

LJGlucagon and epinephrine promote glycogen olysis.

OGlycogenesis is the process of well-fed state.

OGlycogenolysis is the process of Fasting or starvation.

LJBoth these processes are meant for maintaining the blood glucose concentration within the normal range.

inical Significance

Glycogen Storage Diseases

"Glycogen storage disease" is a generic term to describe a group of inherited disorders characterized by deposition of an abnormal type or quantity of glycogen in tissues, or failure to mobilize glycogen.

Glycogen Storage Diseases

Symptoms in addition to exces s glycogen storage:

When a genetic defect affects mainly an isoform of an enzyme expressed in a common symptom is ! . , relating to impaired mobilization of glucose for releas e to the blood during fasting.

When the defect is & difficulty with exer res ult from inability to increase glucose entry into exercise.

- Additional symptoms depend on the particular enzyme that is deficient.

Table 9tx›wtng”Glycdqén storage diseases.

Type I	Von Gierke's disease	Deficiency of glucose-6-phosphatase with glycogen. Hypoglycemia,
Type PIN.		Deficiency of liver phosphorylase kinase High glycogen content in liver, tendency toward hypoglycemia.

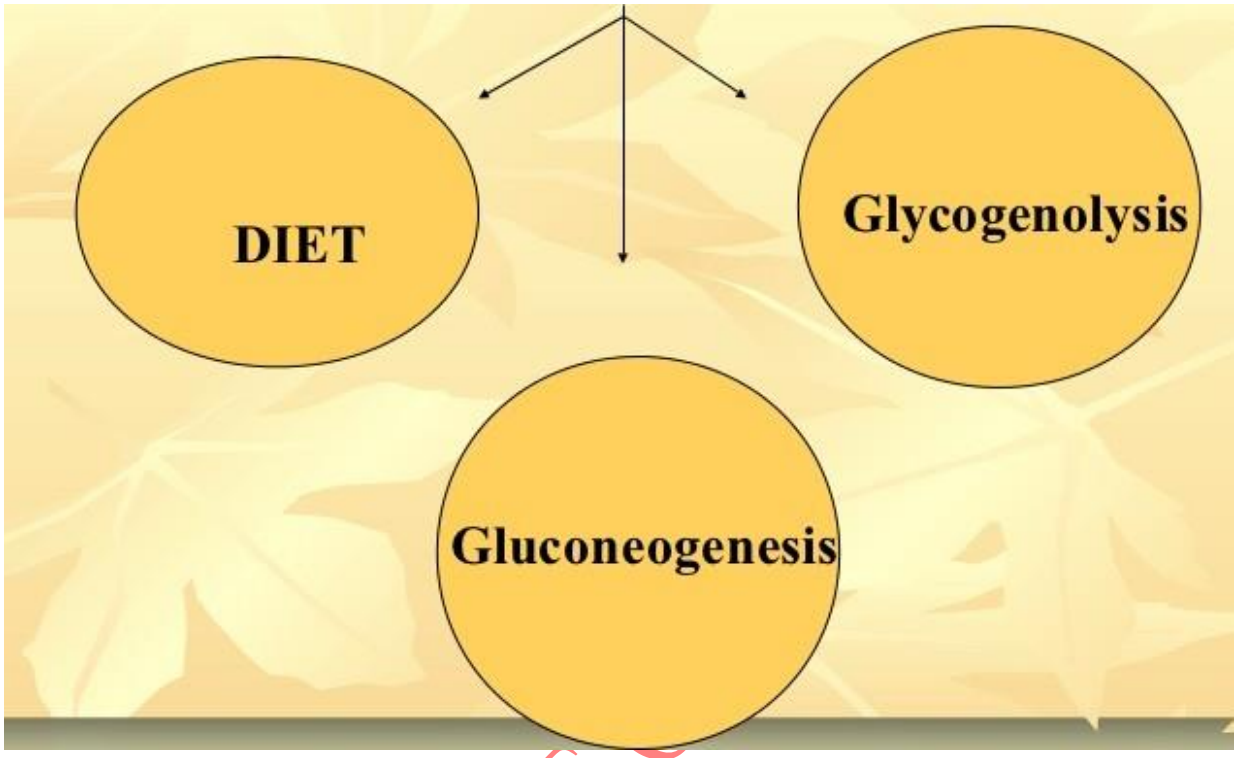
Regulation of Blood glucose

Postabsorptive state: Blood glucose is 4.5-5.5mmol/L.

After carbohydrate meal: 6.5-7.2mmol/L

Durine fasting : 3.3-3.9mmol/L

Blood Glucose



Metabolic $i hormonal mechanisms

regulate blood glucose level

Maintenance of stable levels of glucose in blood is by

- Liver.
- Extrahepatic tissues.
- Hormones

Liver

Freely permeable io glucosc via SLUT-2 iransporicr.

- Passage through cell membrane is raic limiiing

  ^{C}P

- Glucose is phosphorylated by hexokinas c on cniry inio cell

E trahepatic tissues

- Rclaiivcly impcrmcablc io glucose.

- Passage is laciliiaied ihrough › arious enzymes.

Ii has direci c1’1cci on curry o1’ glucose inio ihc cell.

Regulation of blood glucose levels

InsuUn

Anabolic in rcsponse to hypcrglyccmia

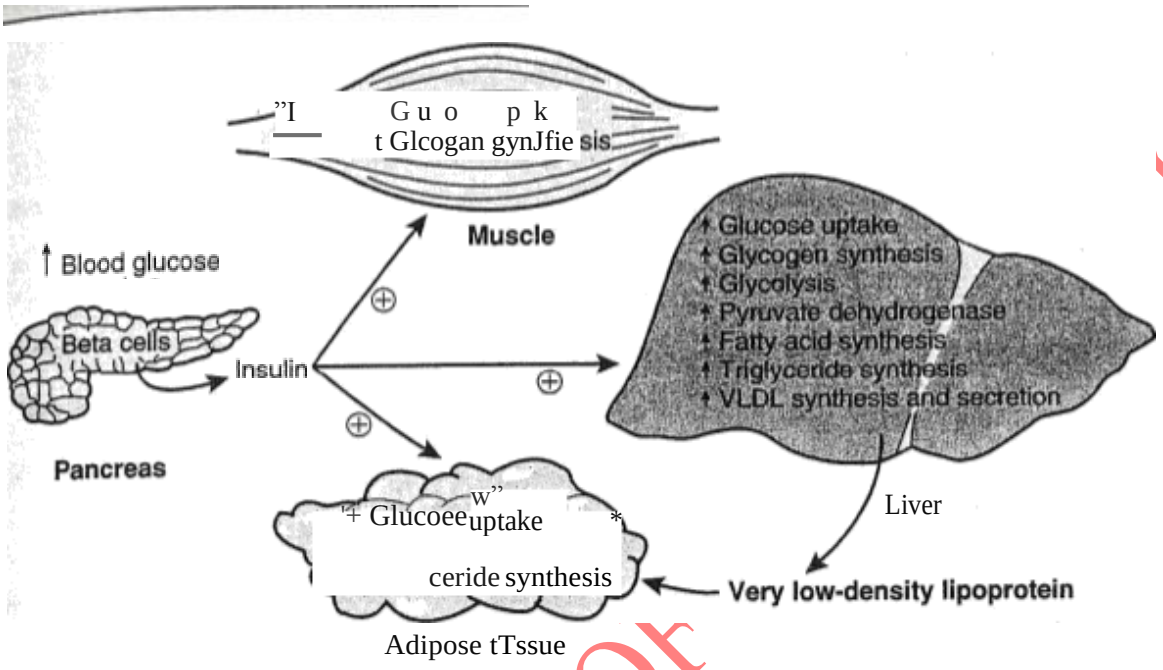
- Siimulaics glycogen synthesis, glycolysis, and fairy acid synihesis

- Siimulaics glycogcn synihesis

Adipose tissue

- Siimulaics lipoproiein lipase rcsuliing in uprate o1’ fairy acids mom chylomicrons and VLDL
- Siimulaics glycolysis for glycerol phosphate synihcsis (precursor io iriglyc erides)

Role in insulin in lowering blood glucose



Glucagon

- Produced by A cells of islets of langerhans of pancreas
- Actions opposite to Insulin.
- Its secretion is stimulated by hypoglycemia.
- It stimulates glycogenolysis & gluconeogenesis from amino acids & lactate.

Regulation of blood glucose levels by Glucagon

Catabolic, in response to hypoglycemia

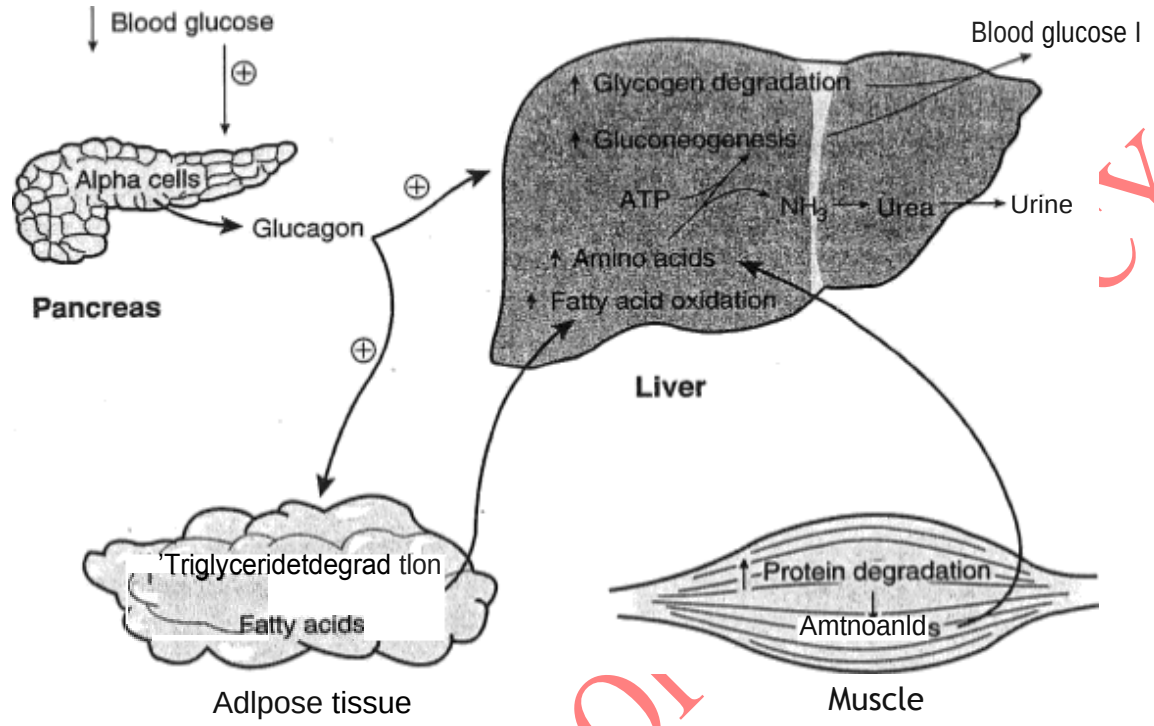
Liver

- Activates glycogen degradation, gluconeogenesis

Adipose tissue

- Stimulates lipolysis and release of fatty acids

Role of glucagon



Role of thyroid hormone

It stimulates glycogenolysis & gluconeogenesis.

H oth o	Hyperthyroid
Fasting blood glucose is lowered.	- Fasting blood glucose is elevated
Patients have decreased ability to utilise glucose.	- Patient utilise glucose at normal or increased rate
Patients are less sensitive to insulin than normal or hyperthyroid patients.	

Glucocorticoids

- Glucocorticoids are antagonistic to insulin.
- Inhibit the utilisation of glucose in extrahepatic tissues.
- Increased gluconeogenesis

Epinephrine

Secreted by adrenal medulla.

" It stimulates glycogenolysis in liver & muscle.

" It diminishes the release of insulin from pancreas.

Other Hormones

Anterior pituitary hormones

Growth hormone:

- Elevates blood glucose level & antagonizes action of insulin.
- Growth hormone is stimulated by hypoglycemia (decreases glucose uptake in tissues)
- Chronic administration of growth hormone leads to diabetes due to B cell exhaustion.

SEX HORMONES

" Estrogens cause increased liberation of insulin.

Testosterone decrease blood sugar level.

Hyperglycemia	Hypoglycemia
Thirsk dry mouth Polyuria Tiredness, fatigue Blurring of vision. Nausea, headache, Hyperphagia Mood change	• Sweating Ttembling,pounding heart Anxiety, hunger - Confusion, drowsiness - Speech difficulty Incoordination. • Inability to concentrate

Clinical aspects

Glycosuria: occurs when venous blood glucose concentration exceeds 9.5-10.0mmol/L

Fructose- 1,6-Biphosphatase deficiency causes lactic acidosis & hypoglycemia..

Diabetes Mellitus

A mulii-organ caiabolic response caused by insulin insu1’1icicncy

- Proicin caiabolis m for gluconeogenesis

sAeei i e

- Lipolysis for fairy acid rcleasc

- Kciogcncsis mom fairy acid oxidaiion
- Gluconeogenesis from amino acids and glycerol

- Kcionuria and caiion excreiion
- Renal ammoniagenesis.

Role of carbohydrates in dental caries

- Fermentable carbohydrates causes loss of caries resistance.
- Caries process is an interplay between oral bacteria, local carbohydrates & tooth surface

Bacteria + Sugars+ Teeth ——— Organic acids

Caries