Bone

Function and Composition

Function:

- Structural role
- Protects delicate tissues
- Provides support for joints
- Serves as a reservoir for ions e.g.
    - Ca^{++}
    - PO_4'''
    - Na^{+}
    - Mg^{+}

Composition:

- Organic ($3/4^{th}$ of bone)
- Inorganic (mineral) – ($1/4^{th}$ vol. of bone) and ½ bone weight.

Minerals:

- Largely (Ca_3PO_4), in addition:
    - CO_3
    - F'
    - OH'
    - Citrate
    - MG^{++}
    - Na^{+}
    - K^{+}

- Bone crystals – hydroxyapatite:
    - Its composition is $CA_{10}(PO_4)_6(OH)_2$ in the form of crystals:
        - Rod shaped
        - $8\text{-}15^{O}$ A thick
        - $20\text{-}40^{O}$ A wide
        - $200\text{-}400^{O}$ long
        - Density 3.0
    - In Hydroxyapatite – other divalent cations can replace Ca^{+}
        - Anions other the phosphate and OH^{-} may be absorbed.

Organic Material: - ~ 90-95% collagen – Type I proteoglycans (small amount in mature dense bed)

- Primary structure is the same as that in skin and tension.

However, has a great mechanical strength – it is denser and less soluble.

- It has ↑ degree of hydroxy lysine and hydroxyproline.
  - ↑ glycosylation of lysine.
  - H^+-bonds between OH pro. stabilise the triple helix.
  - Cross linkes between OH lys and lys stabilize the fibrillar structure.

- A small protein – i.e. osteocalcin (has 3 residues of γ-carboxyglutamate) is present and binds strongly to OH-apatite.

  - plays a role in Ca^{++} regulation in bone and teeth.
  - Vit. K is needed for essential for formation of γ-carboxy Gln residues and may play a role in Ca++ met in bone and teeth) as in blood clotting E).

Structure of Bone:

Bones – 2 types – histologically distinct

Woven Bone:

- Found in embryonic life
- Part of repair process after injury in adults
- Haphazard, non parallel distribution of collagen fiber
- With many randomly distributed bone cells (Osteocytes)
- Formed relatively rapidly weaker than that in adults.

Lamellar Bone:

- Found in adults
- Ordered, parallel arrangement of collagen bundles
- Few, evenly distributed osteocytes.
- Two types:
  - Cortical bone:
    - Most (80%) of skeleton – e.g. shafts of long bone.
    - Dense compsotion
  - Trabecular or cancellous bone – e.g. in vertebra or at the ends of long bones

- Histologically similar to cortical bone
- Porous. Bone tissue arranged narrow spicules.
- The surface area is ~ 5 times greater/ than the cortical bone.

Formation:

- Osteoblasts – make collagen fiber – secrete into ground (of mesenchymal orogin)
  - Become surrounded by bone matrix and are called osteocytes
    ↓ Bone forming capacity.

  - Osteoclasts → involved in bone resorption (contains process of bone remodelling)

  - <u>Mineralization:</u>
    → occurs only in hard tissues.
    → influenced by serum level of Ca^{++} and P' → influence rate of bone formation.
    → serum super saturated with Ca^{++} and p.
    → crystal formation is induced by nucleotion i.e. provision surface on which crystal lattice formation occurs.
    → triple stranded, quarter staggered collagen → serves as nucleating agent.
    → between collagen fibers – in holes ~ 40 mm
    → the staggering of tropocollagen is essential for mineralization.

<u>In Bone Function:</u>

→ Ca^{++} and PO_4''' deposits V OH apatite → increase in crystal size
↓
↑ mineralize serve as incleaing agent.

- However, other tissues have collage → but do not calcify.
  ∴ Other factors involved.

Epithelial Tissue

Epithelial tissues is distributed widely in the body. It is made up of cells that are joined together in the form of sheets, separating the internal spaces of the animal from the exterior. Epithelia can be defined as a sheet of cells that are coherent to each other.

Types of Epithelial cells:

- Keratinizing Epithelial Cells:
    - Keratinocyte of epidermis
    - Basal cells
    - Keratinocytes of fingernail and to
    - Hair shaft cells
    - Hair root sheat cells

- Cells of Wet Stratified Barrier Epithelia
    - Surface epithelial cells of:
        - Tongue
        - Oral cavity
        - Oesophagus
    - Basal cells of epithelia, etc.

- Epithelial cells specialized for exocrine secretion:
    - Salivary gland
    - Mammary gland
    - Sweat Gland
    - Gastric Gland

- Epithelial absorptive cells in Gut, Exocrine and Urogenital trait.
    - Pause border cells of intestine
    - Straited duct cell of exocrine gland
    - Gall bladder epithelial cells
    - etc.

- Epithelial cells serving primarily a barrier function, ling the lungs cyst exocrine gland an urogenital tract.

- Epithelial cells lining closed internal body cavities.

Epithelial cells form a coherent cell street called epithelia, which lines the inner and outer surface of the body.

Absorptive Cells - have numerous harlike microvilli projecting from their free surface to increase the area for absorption:

Adjacent epithelial cells are bound together by functions that give the sheet mechanical strength and also make it impermeable to small molecules. The sheet rests on a basal lamine.

Ciliated cells – celia on their free surface bent in synchrony to move substances (such as mucosa) over the epithelial sheet.

Secretory cells Most epithelial layers have some cells that secrete substance onto the surface.

Secretory epithelial cells are often collected together to form a gland that specializes in the secretion of a particular substance e.g. exocrine glands secrete their product (e.g. tears, mucus and gastric juice) into ducts. Endocrine glands secrete hormones into the blood.

There are on many cases 2 layers of the epithelium – outer layer being the ectodermal and inner layer bring the endoderm.

Melanin

Enmelanine:

- Insoluble
- Heterogenous
- High mol. wt.
- Black to brown heteropolymers of 5, 6-dihydroxyindole and several of its biosynthetic precursor.

Pheomelains:

- Yellow – reddish brown polymers
- High mol. wt.
- Sol. in dil alkali.

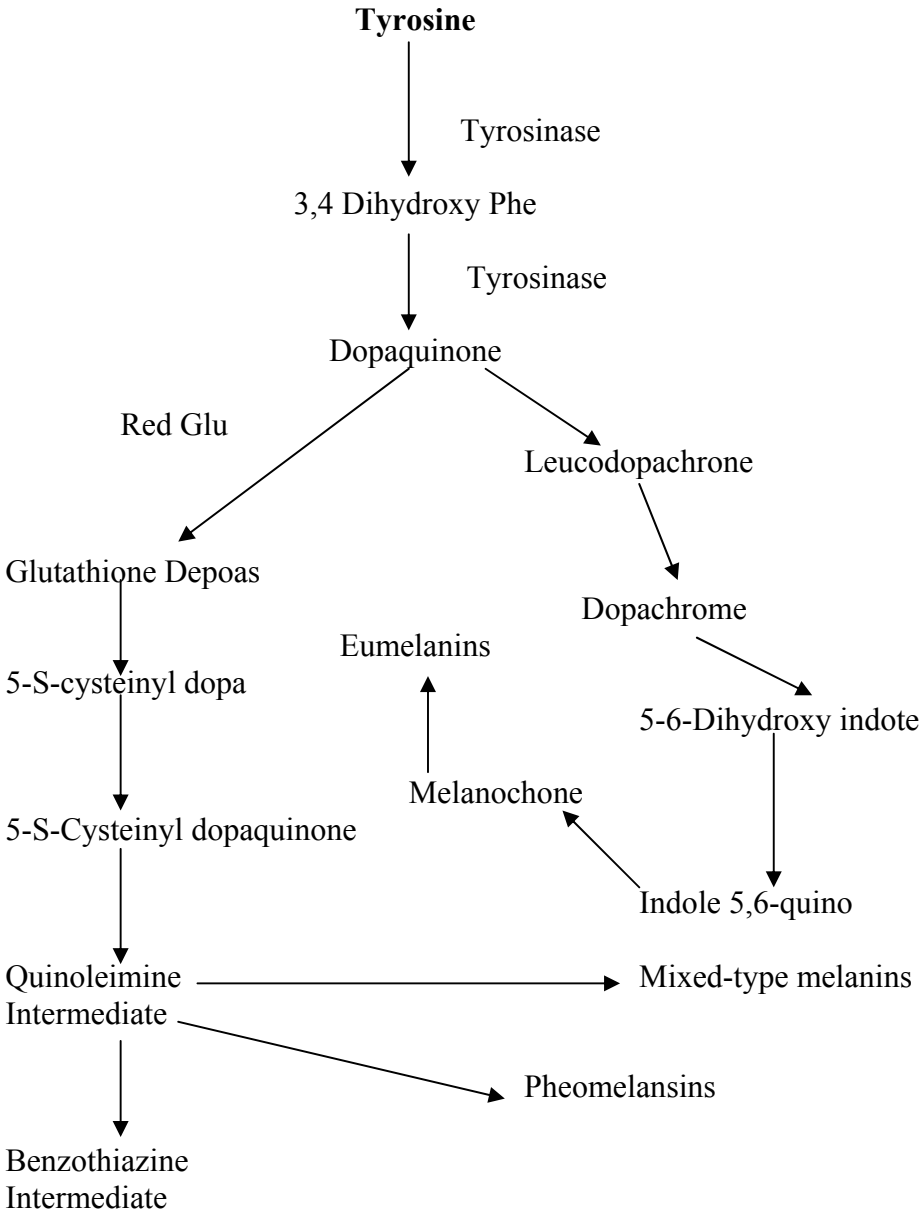
Melakin Biosynthesis -
- Synthesis occurs in melanosomes
- Membrane bond particles with in melanocytes, which are cells of neural crest origin.

- Developing eumelanin polymer entraps free radicals and undergoes partial degradation by H_2O_2 during the auto-oxidative process.

- Pheomelanin and ennalin the complex with protein of the melanosomal matrix forming melanoprotein.

- The pathways is not fully human.

- Synthesis starts from Tyr under the action of tyrosinase, and dependent E.


Tyrosine
Tyrosinase
3,4 Dihydroxy Phe
Tyrosinase
Dopaquinone
Red Glu
Leucodopachrone
Glutathione Depoas
Dopachrome
Eumelanins
5-S-cysteinyl dopa
5-6-Dihydroxy indote
Melanochone
5-S-Cysteinyl dopaquinone
Indole 5,6-quino
Quinoleimine Intermediate
Mixed-type melanins
Pheomelansins
Benzothiazine Intermediate

Metabolic defects of melanin biosynthesis

- Albins:
    - Many clinical syndrome
    - Hypomelanosis – From heritable defect in the pigment cells (melanocytes) of the eye and skin.

- Oculocutaneous albinism → ↓ pigmentation in skin and eye.
    - ~ 10 forms
    - Can be differentiated on the basis of their clinical, biochemical, ultrastructure and genetic characteristics
    - Mostly inherited as Autosomal recessive (some are dominant)

- Tyrosinase - negative albin complete lack of visual pigment melanocytes contain unpigmented melanose.

- Tyrosinase - positive albinos:
    - Have some visible pigment
    - Hair colour ranges from white-yellow to light
    - Hair bulb may contain rightly pigmented melanosomes which convert Tyr → black and melanin.

Ocular albinism:

Both are autosomal recessive and X-linked trait.

The melanocytes of X-linked and heterozygous ocular albines contain macromolecules.

The retinas of female heterozygous for X-linked ocular albinism (Nettleship Variety) exhibits a mosanic pattern of pigment distribution due to random X-chromosome inactivation. The precise metabolic defects leading to hypomelanosis in ocular albinism are unknown.

Outocutaneous albiniodism

- Autosomal recessive trait.

- Patients lack associated nystaymus, photophoto and decreased visual activity.

Muscle

- Major biochemical transducer (machine) that converts potential (chemical) energy into kinetic)mechanism) energy.

- Larger tissue: > 40% of body mass in young adults.
  ~ <30% aged adult

- Needs
  - Constant supply of chemical energy
    ATP and creatine phosphate
  - Means of regulating the mechanical activity:
    - Speed
    - Duration
    - Force of contraction
  - Operator → i.e. the nervous system
  - After use to return to it original state.

- Muscles – 3 Types:
  - Skeletal – striated – under voluntary nervous control
  - Cardiac – Striated –
  - Smooth – non-striated

Structure:

Multinucleated muscle fiber cells – surround by electrically executable membrane - Sarcolemma

Each muscle fiber – contains bundles of many myofibrils arranged in parallel
- Embedded in type of intracellular fluid – Sarcoplasm contains:
  - Glycogen
  - ATP
  - Phosphocreatine
  - E of glycolysis

Sarcoma - Functional units of muscle. It is repeated along the axis of a fibril at distance of 1500-2300 nm.

Under electron microscopy the myofibril has dark and light bands (A bands and I bands).

Central region of A band – less dense than the rest. I band is biseced by a very dense and narrow Z line:

A. Extended

B. Contracted

When cross sections of a myofibril are examined under an electron – it appears that each myofibril is constructed of 2 types of longitudinal filament. One type (the thick filament) – confined to the A band, contains chiefly the protein Myosin ~ 16 nm diameter and arranged in cross section as a hexagonal array.

The other (thin filament) lies in the I band and enters into A bands but not into the H zone of the A bands. These are ~ 6 nm in diameter. They contain proteins actin, tropomyosin and troponin.

In A band, the thick filaments are arranged around the thin (myosin) filament as a secondary hexagonal array. Each thin filament lies symmetrically between 3 thick filament and each thick filament is surrounded by 6 thin filaments.

The thick and thin filaments interact via cross-bridges that emerge at intervals of 14 nm along the thick filament.

- When muscles contract – no change in length of the thick and think filament. However, the H zone and I bands shortens.

- Thus the arrays of interdigititating filaments must slide past one another during muscle contraction. The cross bridges generate and sustain the tension.

Muscles

Muscle structure

Chemical Composition:

- Water 75%
- Proteins:
  - Myosin:
    - Contractile protein
    - Thick filament
  - F.G. Actin
  - Tropomyos - Thin filament
  - Troponin
  - Myoglobin
  - Collagen
- Lipids (~ 30%):
  - Cholesterol
  - Phospholipid
  - TAG
- Carbohydrates - Glycogen ~ 1%
- Other constituents:
  - Phosphocreatine
  - ATP
  - ADP
  - Inorganic:
    - Na^{+}
    - K^{+}
    - Ca^{++}
    - PO4”
    - Son”
- Dipeptide:
  - Carnosine
  - Anserine

  Contain β-alanine
  Function – not known

Contractile proteins involved in muscle contraction:

- Myosin (called thick filament)
- Actin (thin filament) consists of:
  - F & G actin

- Tropomyosin
- Troponin

Structure of Skeletal Muscle

- A skeletal muscle contains fibres, which are arranged in parallel and are surrounded by a thin membrane called Sarcolemma.

- Each fiber:
    - Long
    - Cylindrical
    - Multinucleated cell
    - Cytoplasm – called Sarcoplasm

↓

contains small fibrils called Myofibrils

- A & I bands - Alternating dark (A bands) and light (I bands) on myofibrils. `A' band has a lighter central zone (H zone) while the I band has a dense line (Z-line). A thin dark line called M line is found in the middle of the H zone.

- There is alignment of the corresponding bonds of adjacent myofibrils. And the area bounded by two adjacent Z lines is a myofibril is called the Sarcomere

- IN the I band – greater portion of thin filament.

- A band – Thick filaments and ends of the thin filament.

- Diameter of thick filament about twice that of a thin filament.

Structure of myosin molecule and myosin filament

- Myosin:

    - 2 intertwined and helics, each with a globular head at its C-terminus.
    - 2 light chains are located near the globular head

- A myosin filament (Thick filament) is formed by symmetrical aggregation of many myosin molecules on either side of the M line.

Cleavage of Myosin Molecular by Trypsin and Papain

- Cleavage at special site
  e.g. Trypsin produces:
    - Heavy meromyosin:
      - Globulin head
      - Par of chain
    - Light meromyosin chain

  Papin – Digest heavy meromyosin:
    - S1 :
      - 2 globular heads
      - + 4 light chain
    - S2:
      - The rest of the heavy meromyosin

  The LMM – HMM and S1-S2 functions are the flexible regions of myosin.

Structure of thin filament

- Consists of:
  - F-actin double helix.
  - Tropomyosin double helix
  - A troponin system

- Actin occurs in 2 forms:
  - F-actin (Fibrous)
  - G-actin (globular)

- Two F-actin chains form a intertwined double stranded helix with a shallow groove between them. Each turn of this helix contains 14 polymerised G-actin molecules.

- F-actin contains myosin-binding sites on its surface.

- Tropomysin has 2 long filamentous intertwined double-helix that fits into the groove of the F-actin helix. At rest the tropomyosin lies at the end of this groove.

- Troponin system consists of complexes of globular proteins that are found at regular intervals along the F-actin helix.
  (with 12 G-actin molecules between two complexes).

- Troponin complex found only in skeletal and cardiac muscle. Each as 3 subunits:

  T, C and I:
  - C - bind Ca^{++} ions (each has 4 Ca^{++} binding sites)
  - T – binds to tropomyosin
  - I – inhibits binding of myosin to actin.

The sarcotubular system

Membranous system has 2 major components:

- T system (Transverse tubules)
- Sarcoplasmic reticulum

(a) The Transverse tubules – so called they are arranged at right angle to the long axis of muscle fibers.

- They are in vaginations of the sarcolemma into the myofibrils between the A & I bands.
  Each sarcomere – 2 T-tubules.

- The T-tubules make contact with the Sarcoplasmic reticulum and they ensure rapid transmission of action potential at all fibrils.

(b) The Sarcoplasmic and Reticulum

- Specialized portion of smooth endo-plasmic reticulum – surrounds each myofibril.

- Surround each myofibril.

- Stores Ca^{++} - and has a Ca^{++} presence in its membrane of a Ca^{++} - stimulated ATPase.
  This ATPase can release Ca^{++} into the sarcoplasm and withdraw then actively into the sarcoplasmic reticulum. ATP is the source of energy for Ca^{++} withdrawal.

- Also contains a protein called Colsequestrin – Binds more than 40 calcium ions/mol. (store for Ca^{++}).

  Ca^{++} is normally stored in the cistern of the sarcoplasmic reticulum, which are situated near the transverse tubules.

B-Muscle Contraction

1. Actin-binding sites are covered with tropomyosin when muscle is at rest. These binding sites are on F actin and bind myosin head during muscle contraction.

2. Arrival of Actin Potential

   When a action potential arrives at the sarcoleuma and Ca++ is released into the sarcoplasm tropomyosin moves deeper into the actin groove –
   Actin-binding sites are exposed, which bind myosin heads to form – Actomyosin complexes.

Energy of ATP origin is released and thin filament slides along the thick filament. This sliding motion shortens the sarcomeres and results in muscle contraction.

3. End of contraction

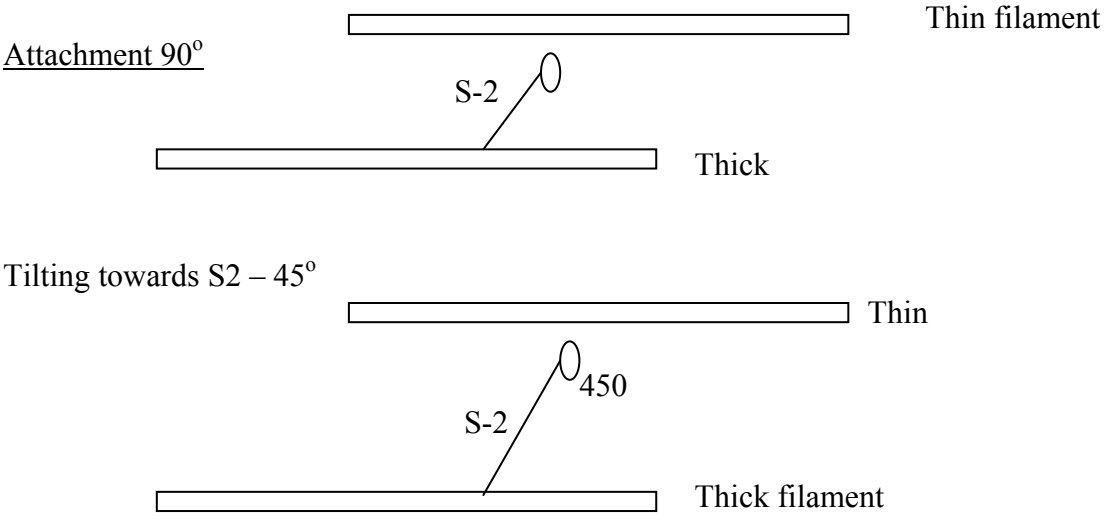
When contraction ends:

1. Ca^{++} ions withdrawn from the sarcoplasm into the sarcoplasmic reticulum.
2. Myosin is detached from actin.
3. Tropomyosin returns to resting position.

4. Changes in the position of myosin heads in muscle contraction

When myosin heads are attached to the actin filaments just before the beginning of contraction, the long axis of the subunits are initially per pendicular (90) to the thin actin filament. A conformational change occurs which fills the myosin heads at 45 toward their S-2 segment. Tilting the myosin heads, pulls the actin (thin) filament along the myosin (thick filament).

The myosin heads are detached from the thin filaments as the sliding movement begins.



5. Role of ATP in muscle contraction

- Myosin heads have ATPase activity.
- Each makes up 2 ATP and hydrolyses it at its active site at the end of each muscle contraction.
- The energy, ADP and P is produced only after the myosin heads are attached again at 90° to the actin filament.
- Actin enhances the release of 3 products of ATP hydrolysis from the myosin heads (also attracts ATPase at the end of contraction).

Riger Motis – After death ATP is completely depleted and myosin head can no longer be detached from actin – permanent state of muscle contraction – "Rigor Mortis"

Regulation of Muscle Contraction

Two mechanisms:

- Actin-based regulation
- Myosin-based regulation

Both require Ca^{++}.

Actin based regulation – involves:

- Ca^{++}
- Troponin system

(i) When muscle at rest - Ca^{++} in sarcoplams (~ 10^{-7} mol/l at rest)
(as mostly confined to sarcoplasmic reticulum by an active transport).

(ii) Arrival of action potential – at sarcollama

- Rapidly transmitted to all myofibrils by the T-system.
- Ca^{++} release from western of sarcoplasmic reticulum.
- ↑ Ca^{++} in sarcoplasm (10^{-5} mol/l)
- Causes saturation of 4 binding sites of each trponin C.

This causes following changes:

1. Change in the conformation of the troponin.
2. Movement of tropomyosin deeper to active groove.
3. Exposure of actin binding site.
4. Actomyosin interaction.
5. Change in conformation of myosin.
6. Muscle contraction.

(iii) Following contraction

- Sarcoplasmic calcium ion withdraw into the system of the sarcoplasmic reticulum by Ca^{++} ATPase and bind to calsequestion.
- Removal of Ca^{++} from Troponin C.
- Tropomysin moves to cover the actin binding sites.
- ↑ binding of myosin by Troponin-I.

II. Myosin-based regulations

- occurs in smooth muscles.
- Lack troponin system (poorly developed sarcoplasmic)

Involves:

1. P light chain.
2. Myosin light chain kinase (phosphorylates p light chain and contains caluodulin, Ca^{++} binding protein)
3. Ca^{++}
4. A phosphatase enzyme.

Smooth muscle myosin interacts with actin when p-light chains is phosphorylated by myosin light chain kinase. Colmodul bond to myosin light chain kinase. Stimulation of muscle by an action potential - ↑ Ca^{++} in sarcoplasm

↑ binding of Ca^{++} to calmodulin

↓

Activates myosin tight chain kinase allosterically.

↓

Phosphorylates p-light chain to bring about interaction between myosin and actin and the subsequent contraction.

At end of contraction

- Withdrawal of Ca^{++} from the sarcoplasm
- Phosphate group of the p-light chain and removed by phosphatase.

Muscle Contraction

Arrival of action potential

↓

Transfer across the synopse by release of acetyl choline

↓

Binds to acetylcholine receptors

↓

Propagation of action potential along sarcolemma

↓ (has Na+, K+, ATPase)

Signal to transverse tubules (system)

↓ (uraginates into muscle anterior at Z line) and makdes contact with cisternae of sarcoplasmic reticulum

Discharge of Ca^{++} from cisternal

↓

Ca^{++} in cytosol of muscle [10^{-8}M 10^{-5}M]

↓

Binds to Tn-C site

↓

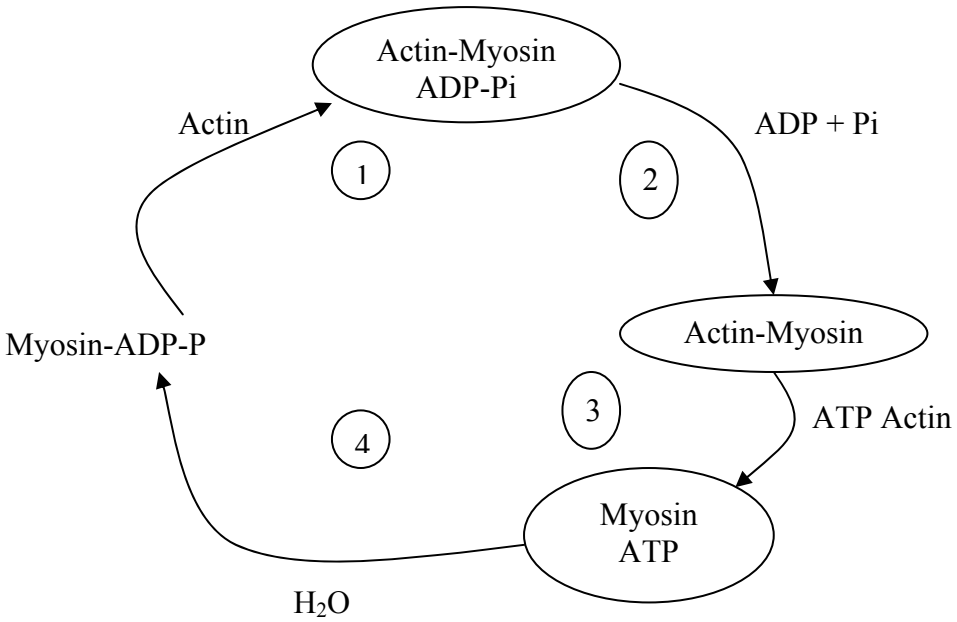
Contraction

Rowboat Model

V. rapid
3 millisecond to Ca^{++}

and peak

Energy of this process comes from ATP



Regulation by Myosin Kinase

- Tropoin-Tropomyosin – Actin system major means for regulation of skeletal muscle contraction

  In other muscles – other regulations.

Source of Energy for Muscles

Resting Muscles

- Need constant supply of ATP for const. composition and metabolism
- ATP from ↑ FA carbohydrates acetoacetate and a.c.
- Stored as creatine phosphate
  ATP is about 25 times Cr. p at the
  ADP Cr.

  and conc. of Mg^{++}, K^{+}, H^{+}

  Stores glycogen ($3/4^{th}$ of total body glycogen)

- In testing muscle 3-8 times more Cr. than ATP
  (for ~ 30-100 contraction)

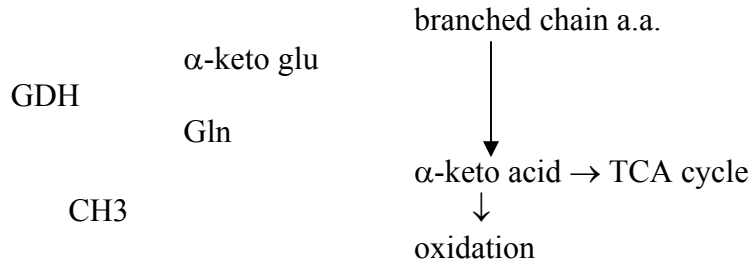
- When there is a de for ATP

$$2\ ADP \xrightarrow{\text{Adenylate kinase}} ATP + AMP$$

AMP - Glycolysis

- When ↓ denad for ATP, then the reverse reaction is ↑.

- Energy from glycolysis, branched a.a.



(ii) Deamination of AMP to inosinic acid produce NH_3 by adenylate deaminase.

NH_3 useful :
- to convert Pyr to alanine
- to buffer the acidity produced by lactic acid

Pyr + NH3 alanine

Transamination

Pyr + a.a. alanine + α- keto acid

Alanine + lactate Glucose

Blood

Muscle Liver

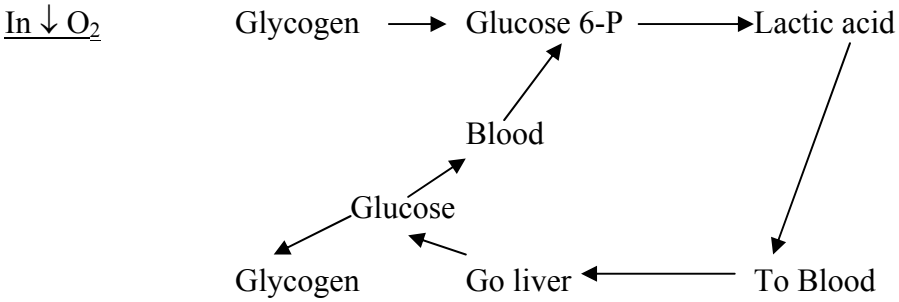
Glucose

- Alanine cycle
- Cori cycle

Glycolysis during muscle contraction muscle retains glucose, its preferred fuel for bursts of activity.

↑ glycolysis and glycogen break down

→ ↑ ATP for contraction



Red muscles and cardiac muscles have high rate of oxidation phosphorylation.

The ability of muscles to sustain maximal activity anaerobically leads to the accumulation of an oxygen debt.

Red muscles ⟶ oxidative phosphorylation

Cardiac muscles:

- Aerobic reactions to get ATP
- ↓ Glucose utilization in normally
- ↑ FA and some acetoacetate and lactate

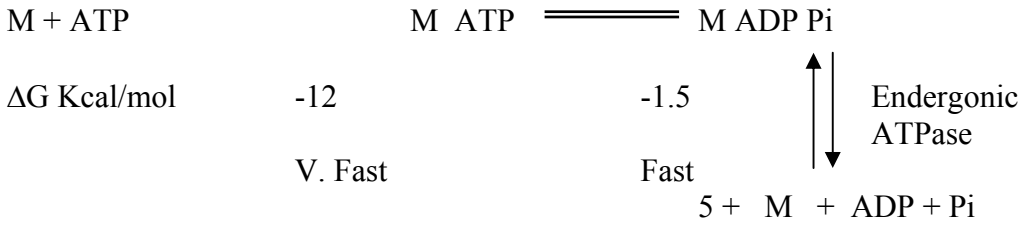
↑ contraction→ ↑ blood glucose utilization
↑ lactate

Role of ATP in Contraction

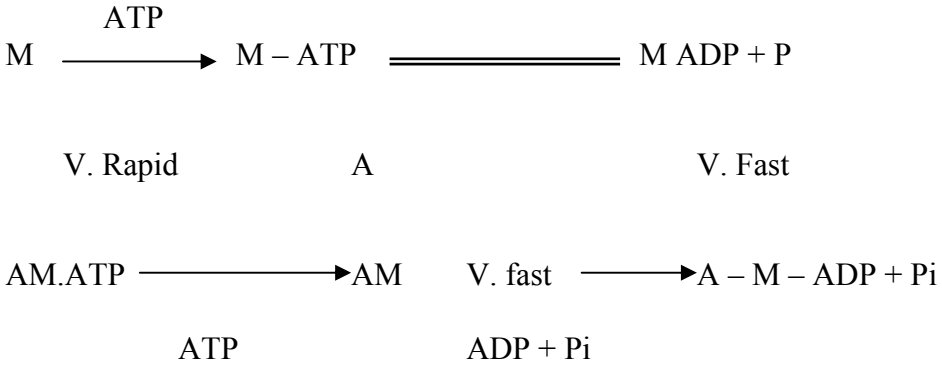
ATP provides energy for cross bridge between myosin and actin.

ATPas in the globular domain hydrolysis it.

In absence of Actin



In presence of actin



- Actin binding enhances myosin ATPase about 300-400 fold and ∴ permit dissociation of ADP + Pi (in actomyosin).

In resting muscle

Tropomyosin blocks interaction of actin and myosin.

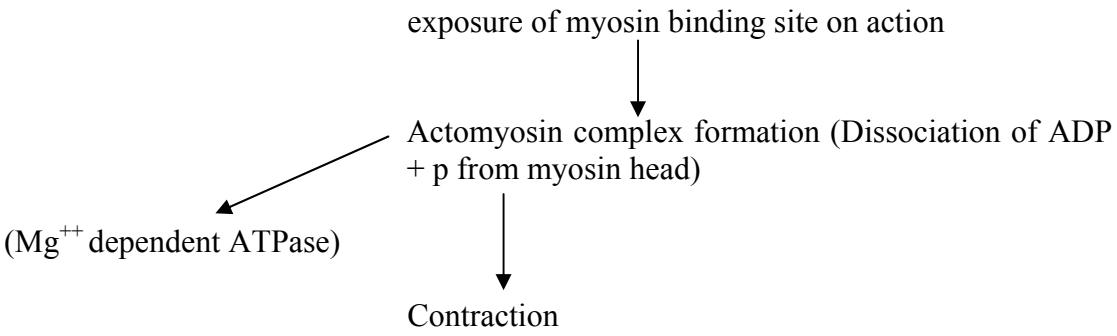
- Ca^{++} addition ⟶ binding to Tn-C undergoes conformational change (Strengthen the interaction between Tn-C, Tn I and T—T).

∴ ↓ link between Tn-I actin

↓

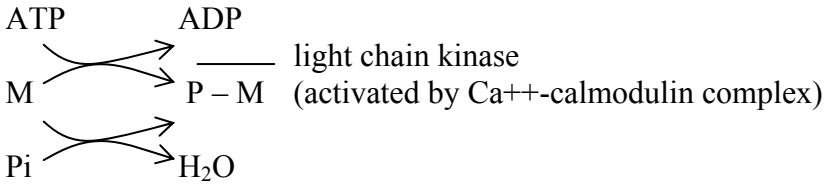
Tropomyosin moves into groove

↓

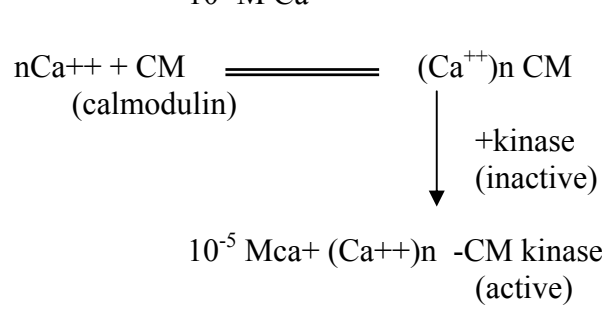


Actin-myosin-Tropomyosin-Tropomin complex behaves as a Mg^{++}, Ca^{++}-dependent ATPase.

e.g. Myosin kinase (light chain)



Phosphatase as follows



(This is not a major imp. in skeletal and cardiac muscle contraction)

<u>Role of Sarcoplasmic retatin in Relaxation</u>

Gath (has 1 ATP band) – water vol. globular protein)

Actin – activates the myosin ATPase which catalyses ATP hydrolysis at a rather slow rate at physiological pH and Mg^{++}.

Tropomyosin – rod shaped ~ 41 mm long.
- consists of 2 nonidentical and helical polypeptide chains two- around each other in a coild lies near the groove of actin.

Tropoin - contains 3 different subunits T, I, C.

Muscle Disorders

- Disease affecting the musculo skeletal system
    - rheumatoid arthritis

- Systemic disease manifested by pain in the muscles e.g. polymyalgia rheumatica

- Diseases affecting the internal organs, skin and musculo-skeletal system
    e.g. systemic lupus erythematosus.

- Muscular dystrophies

- Other metabolic diseases

- Biochemical abnormalities

- test for muscle diseases:
    - Serum
    - Urine
    - Other special tests

- Normal muscle structure

- Composition

- Function (contraction)

- Ca^{++}
- ATP creatinine (p)
- Presence of carnorine

The cardiovascular system

- Structure of heart

- Regulation of cardiac function

- Investigation of C.V.S.

- Clinical manifestations
- Clinical findings
- Laboratory diagnosis
- Biochemical findings in different heart diseases

THE NERVOUS TISSUES

Makes about 1/40th of total body wt. of the body:

- Brain
- Special cord
- Cranial and spinal nerves and their ganglia and plexuses
- Autonomic nervous system

NS Controls:

- Rapid activities of the body e.g. muscular contraction
- Rapidly changes visceral events
- Changes rate of secretion of some endocrine glands

↓

Regulates metabolic functions

- V. unique

- Receives thousands of bits of information from different sensory organs and integrates them together to determine the response to be made by the body.

- Nervous system is a network of living fibers that interconnect with each other and with other cell types e.g. sensory receptors, muscles, secretory cells etc.

    - Small gaps present between these cells.

    - Communicate by signaling from one cell to another (Transmission)

General Design of Nervous System

1. The sensory division – sensory receptors

    - Visual receptors
    - Auditory receptors
    - Tactile receptors
    - or other kinds of receptors

    - Most activities of nervous system originates by sensory experience coming from sensory receptors.

    - This sensory experience may cause immediate reaction or may be stored to determine some body reaction some time in future.

Somatic Sensory Axis of the Nervous System

Sensory receptors ⟶ spinal nerves ⟶ conducted to all segment of CNS.

2. The Motor Division – the Effectors

- Most important function of nervous tissue - Control of body activities

Controlling by:
- Contraction of skeletal muscles
- Contraction of smooth muscles in internal organs
- Secretion of both exocrine and endocrine glands

These activities are together called - Motor

Functions of the nervous system and the muscle and glands are called the Effectors

- as they perform the function of dictated by nervous signal.

Motor axis of the nervous system

3. Processing of Information

Nervous system – processes incoming information

- So appropriate motor responses occur ~ 99% of sensory information is discarded by the brain as unimportant e.g. clothes we wear, etc.

- Important things around us. Pressure of seat. Selected sensory information is channeled proper regions of the brain to cause desired responses e.g. placed on hot stove – Quickly move away from stove.

- Synopses play an important role in processing information:

  Synopses is the junction point from one neuron to the next and ……. is an advantageous site for control of signal transmission.

  Synopses (Selective Action):

  - Determine the direction in which the nervous signal will spread.

  - Some transmit signals from one neuron to other with ease, while others do so with difficulty.

  - Activity may be facilitory /inhibitory

  - May block weak signals allowing the strong signal to pass

  - May channel the signal in different directions

  ∴ Synopses are very important in processing information

4. Storage of Information – Memory

- Only small portion of sensory information can cause immediate motor response.

- Much is stored for future control of motor activities and for use in the thinking processes.

- Storage occurs mainly in cerebral cortex.

- Some storage:
  - basal regions of brain
  - spinal cord

- Storage process – known as memory.

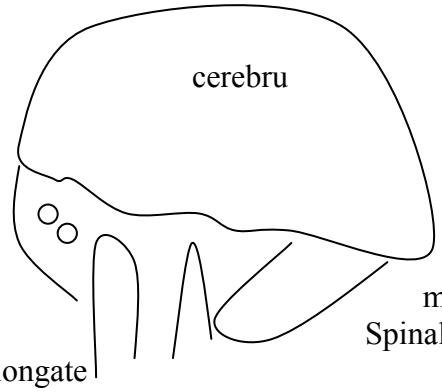
- Also the function of synopses i.e. if a sensory signal is passed through the synopses, then the synopses becomes more capable of transmitting the same signal the next time. This process is called facilitation.

- Once memory is stored in the nervous system, it becomes part of the processing mechanism.

Sensory (afferent)neurons – Transmit impulses from various sense organs to the brain and spinal cord.

Motor (efferent) neurons – Transmit impulses from the brain or spinal cord to muscle (cause contraction) or to glands (stimulate secretion).

Interneuron (associative) neuron – Make connection between sensory, motor and other associate neurons.



VS - Automonic nervous system - Controls internal involving function (heart beat, secretion digestion, joints, etc. emotions, sweat rate, size of pupil of the eye)

- Central Nervous System:
  - Brain
  - Spinal cord
  - Nerves
- Sense Organs

The three major levels of nervous system

Function:

3 Major levels with special functional significance:

- The spinal cord level
- The lower brain level
- The higher brain or cortical level

Spinal cord level:

- Has many segments.

- Sensory signals are transmitted through the spinal nerves into each segment – cause localized motor responses either in the segment of the body in which the sensory information is received or in adjacent segments.

- All spinal cord motor responses are automatic and occur instantly in response to the sensory signal – They occur in specific pattern of response called reflexes.

  e.g.

Muscle stretch reflect

Spindle sensory nerve receptor → Sensory → To spinal cord → Motor neurons

Nervous impulses

Muscle stretches suddenly → Transmit impulses

(effector causes contraction)

This reflex acts as a feedback mechanism operating from a receptor to an effector.

- Cord can function even after the brain is removed.

(2) Lower Brain Level – Controls most of the subconscious activities of the body. It is composed of:
  - The medulla
  - Pons
  - Mesencephalon
  - Hypothalamus
  - Thalamus
  - Cerebellem
  - Basal gangha

e.g. Subconscious control of arterial BP. and respiration (medulla and pons).
- Control of equilibrium (cerebelum and medulla, pons and mesencephalon).
- Turning of head and eyes
- Emotions

- This level operates usually but not always below the conscious level.

(3) The Higher brain or cortical level

- A vast information storage area.
- Has ~ ¾ of all the neuronal cell bodies.
- Store memories of past experience.
- Patterns of motor responses are stored.
- Cerebral cortex connected to thalamus.
- Activation of thalamus activates cerebral cortex.

Also activation of regions in the mesencephalun ⟶ Transmit diffuse signals to cerebral cortex (partially through the thalamus)

i.e. Wabefulness

Inactive regions of the mesencephalon ⟶ Thalamic and cortical region become inactive (sleep)

- Some parts of cerebral cortex (i.e. prefrontal lobe and temporal and parietal lobes) are in thinking.

Destruction of large areas of cerebral cortex may not block some of the conscious activities of the body.

Function of neuronal synopses

Information is transmitted in the CNS in the form of nerve impulses through a succession of neurons one from another.

These impulses:
- may be blocked into transmission from one neuron to another.
- changed from single impulse to repetitive impulses.
- integrated with impulses from other neurons to cause highly intricate patterns of impulses in successive neurons.

These functions are classified as synoptic functions of neurons.

Physiological anatomy of synapse

Synapse – function between neurons.

On the motor neuro (in the anterior horn of the spinal cord) ~ 6000 or more small knobs are present on the surface of dendrites and soma – These are synaptic knobs. ~ 80-90% on dendrites.

These are terminal ends of nerve fibrils that originate in many other neurons and usually not were than a few knobs are derived from any single previous neuron.

- The synaptic knobs are either:

    - Excitory – secrete a sub. that excites the neurons.
    - Inhibitory – secrete a sub that inhibits a neuron.

- Neurons from different part of CNS differ from the motor neurons:

    - Size, length, no. of dendrites (some as long as 1 meter).
    - length and size of axon
    - size of cell body
    - no. of synaptic knobs (a few – 100,000)

∴ different neurons reacts differently to incoming signals in different parts and perform different functions.

<u>Synaptic knobs</u>

The knob has two internal structures, imp. for excitatory and inhibitory function of the synapse.

- Synaptic vesicles – contains transmitter substance

    ↓

    when released into synaptic cleft:
    either:
    - Excites or
    - Inhibits (neurons)

- Mitochondria

    |

    provides ATP for synthesis of new transmitter substances (synthesis v. fast)

    - Excites if the neuronal membrane contains excitatory receptor.
    - Inhibits if inhibitory receptors

- When an action potential spreads over a synaptic knob, the membrane depolarization causes emptying of a small number of vesicles into the cleft and release of transmitter substances – change permeability characteristics of the neuronal membrane – lead to excitation or inhibition of neuron depending on the type of transmitter substance.

Mechanism by which the synaptic knobs action potential causes release of Transmitter vesicle

- Ca^{++} plays a role.

- Spread of action potential over the membrane of the knob – causes Ca^{++} (small amount) to leak into the knob. It attracts the transmitter vesicles to the membrane – causes rupture – spillage of their content into the synaptic cleft.

  e.g. ~ 300 mol. of acetylcholaine in each vesicle – enough synaptic knob on neuron to cause transmission of 100,000 impulses.

- New transmitter sub. are continously synthesised in cytoplasm of synaptic knob – immediately transported into the vesicles and stored needed.

Action of transmitter sub on postsynaptic neuron

Transmitter binds to specific receptor mol. ( ) in the membrane of neuron – increase the membrane permeability esp. to:

- sodium ion when the membrane receptor is excitary.
- ↑ permeability to K^+ and Cl^- when the receptor is inhibitory.

Chemical and physiological Nature of the transmitter substances

The action of many nerve pathways is mediated by a chemical substance (e.g. transmission of nerve impulse from a nerve to an effector skeletal muscle occurs a myoneural function i.e. the area where a motor nerve terminates a skeletal muscle fiber.

- Excitation and inhibition depends on the nature of transmitter and nature of receptor in the post synaptic membrane e.g.

  - Some neuron may be excited by acetyl choline – but other inhibited by glycine – while others are excited.

    e.g. Norepinephrine – causes inhibition or excitation

  - Duration of stimulation produced by a transmitter substance – are also different e.g. 10-20 milli second – 200-300 milli seconds.

  - Some transmitter;
    - ↑ firing rate of neurons

- change the neuroons sensitivity to other transmitter substance. These are called modulators.

- A single neuron releases only one type of transmitter.

Structure:

- Nervous tissue has a lobillion nerves.

- Mostly located in brain.

- The brain contains of – few types of cells ~ 10^{10} neurons or nerve cells and glial cells.

- Each neuron is connected to several hundreds even thousands of other neurons by synapses.

- At each moment each neuron may either signal or not signal based on the integration of its inhibitory and excitatory stimuli.

- Each neuron has a cell body (a swollen portion of the neuron) – abundant cytoplasm and large centrally located nucleus.

- The long extension of cytoplasm that conducts the impulse away from cell body is called the axon.

- Short aborized extensions of cytoplasm that receive impulses from other neurons are called dendrites or dendrous.

- Neurons are protected by various types of tubular structures (e.g. myelin sheath) – not a part of neurons.

- Composition of cytoplasm in the cell body and the extension of the cytoplasm are different:

  Cell body cytoplasm has:
  - Golgi apparatus
  - Mitochondria
  - Pigment granules
  - Droptlets of lipid and glycine
  - Neurofibrils
  - Neurotubles
  - Neurofilament
  - PER
  - Microfilaments

  Axon cytoplasm:
  - Neurofibrils

    - Mitochondria
    - No ER, pigment or lipid

- In dendrites and axons – NO ER ∴ No protein synthesis.

- Protein synthesis in cell body and transmitted to axons and dendrites.

    - Gray matter:
        - cell bodies of neurons their dendrites
        - Proximal portion of the axons
    - White matter - Devoid of cell bodies and heavy investied with myelin.

Summary of Nerve Cell Types

Neurons: Neurons may have large or small cell bodies – Perikarya.

They possess a large nucleus containing nucleolus and have a high content of ribosomes in cytoplasm attached to endoplasmic reticulum and also have a high mitochondria content.

These features are necessary for active synthetic secretory activities and for large capacity for energy production.

They also possess prominent processes forming extensions of the outer cell membrane – axons and dendrites.

They have an excitable character.

Glial cells

They do not possess the excitable characteristics of the Nerve cell. They are smaller than neurons and also possess processessing coming out from their cell bodies.

They are of 3 types:

1. Astrocytes – make contact with blood capillaries and are important for deriving nutrients from the blood.

2. Oligodendroglia – They produce myelin sheath of the axon.

3. Schwann cells – myelinate peripheral nerves outside the brain.

Generally, the glial cells are thought to have a supportive role.

Composition of Nerve Tissue

- Gray matter (conc. of nerve cell bodies) - ↑ water than white matter

- White matter – (Nerve fibers).

Both mixed	-	78%	(Water conent of myelin 40%,
Cord	-	75%	white matter 70% and gray matter 80%).

Solids of the nerve tissues

Proteins

- Constitute ~ 38-40% of the total solids

- Incude globulins, nucleoproteins and a characteristic albuminoid called neurotaratin

(1) S-100 (May play a role in memory or learning ability of brain?)

- Acidic protein – has ~ 30% Glu and Asp.
- In large amounts in Glial cells of brain and in small amounts in neurons.
- Has affinity for Ca^{++}.
- Undergoes conformational change in presence of Ca^{++}.

(2) 14-3.2

- Highly acidic protein found in neurons.
- It is an isozyme of enolase.
  (ctalyses the reversible conversion of 2-phosphoglycerate to PEP).

(3) Calmodulin:

- Ca^{++} binding protein.
- Necessary for Ca^{++} activation of the enzyme cyclic nucleotide phosphodiesterase.

cAMP $\xrightarrow[\text{calmodulin phosphodiesterase}]{Ca^{++}}$ 5'-AMP

- Involved in Ca^{++} dependent release of acetyl cholaine and norepinephrine from the stores (vesicular)

Norepinephrine (in vesicles of cytoplasm of axon) $\xrightarrow[\text{calmodulin}]{Ca^{++}}$ Norepinephrine (Discharge from axon)

In Myelin
- proteins are basic proteins and - rich in Arg
- Proteolipid - protein and lipid

Lipids: ~ one half of solid content (51-54%).
- High lipid content in nervous tissue.
- Myelin, white matter and gray matter lipid content: 80, 60 and 40%.
- Most compound lipids, e.g. phospholipids, cerebrosides or galactolipid, S containing lipids, aminolipids.
- Cholesterol - ~ 25% of the total body cholesterol in the nervous tissue. Cholesterol is synthesised in the brain and has a very low rate of breakdown or turnover number.
- FA - synthesised in brain.
  - comp. is constant (some variation occur with diet)
  - Mostly insaturated long chains of C. ~ 24 C.

No metabolic rate has been assigned to the lipids found in NT other than that of cellular membrane function.

Metabolism of Nervous Tissue

Carbohydrate
- in well nourished animal glucose – completely oxidised to CO_2 + H_2O
- ~ 25% of O_2 consumption is due to glucose oxidation in brain.
- ↑ rate of TCA cycle. Very little lactate.
- ↑ anoxia → ↑ rate of glycolysis and lactate formation possibly by activation of PFK and HKS
  PFK also activated ny NH_2^+
- ↓ glucose – blood – Dangerous for brain. Small amount of endogenous glycogen can supply glucose.

*Sudden removal of glucose – cerebral failure.

*Long term hypoglycaemia – No cereebral failure.

Due to utilizationof KB utilization

↑ conc. of KB in blood - ↑ KB utilization by brain

- Control of synthesis and breakdown of brain glycogen same as that observed in other tissues.

- Insulin has no effect on brain glucose or glycogen met. Insulin does not cross the blood brain barrier.

- ~ 3-5% of glucose is met by HMP to provide NADPH for cholesterol and FA synthesis.

A.A. Met

- Brain has high free a.a. content.
- ~ 8 times as high as in plasma and conc. of individual a.a. also different.

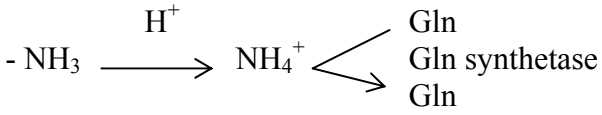
  e.g. Glu and Asp ~ 300-fold greater than in plasma.

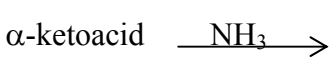
- γ-aminobutyric acid, N-acetyl as p. and glu are present in high amounts.

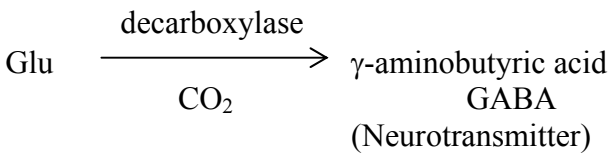
- Rate of a.a. uptake by brain is low:

  3-carrier:
  - Neutral a.a.
  - Basic a.a.
  - Acidic a.a.

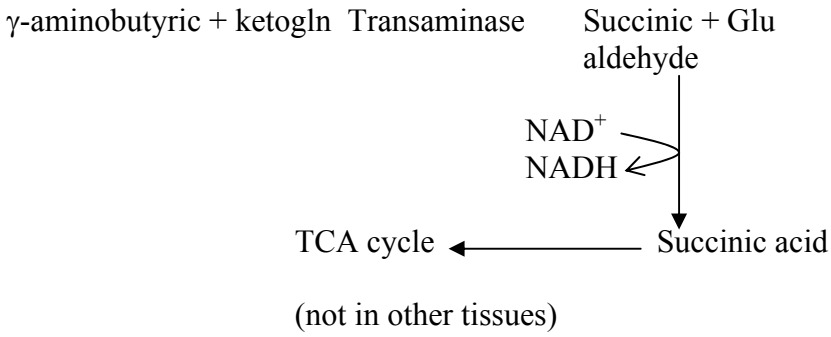
- However, brain can retain and reutilize N for a.a. synthesis.







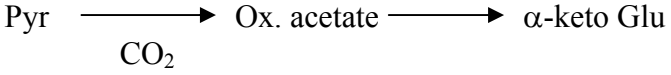
*Catabolismof GABA – GABA shunt



(not in other tissues)

- Glu and Asp - ↑ cAMP formation from ATP in brain.
  Two cAMP dependent protein kinases stimulate protein phosphorylation and in the synaptic membrane this phosphorylation is imp. for the transmission of nervous impulses.

- CO_2 fixation - When ↑ NH_3. TCA cycle depleted of α-keto Glu



- A small amount of urea formation.

Nucleic Acid Met.

Large were cells – produce nuclic acid actively.

- Brain cannot synthesise pyr. but can sym. purine bases and purine salvage pathway is the major one for sym of GMP, IMP and AMP.

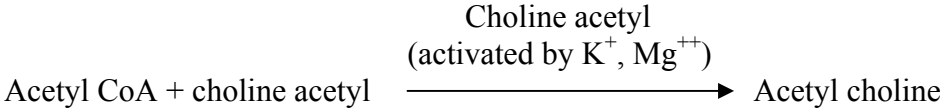
FA

- Synthesis of long chain FA, cholesterol.

Some important transmitter substances

~ 30 different CNS transmitters.

(1) Acetyl choline



(in cytoplasm of cholinergic type of synaptic kbob)

- Between post and pre-ganglionicfib of aminic N.S. and all postganglionic parasympathetic and some postganglionic sympathetic endings.

$CH_2.COO.S.CoA + (CH_3)_3N+.CH_2.CH_2.OH$

Acetyl choline esterase (found in nerve endings and within nerve fibers)

- Acetyl CoA
- CoASH
- H_2O

$CH_3.CO.O.CH_2.CH_2N+(CH_3)_3$ Acetyl choline

- fibers utilizing acetyl choline as mediator are referred to as cholinergic.

- Nerve impulse arriving at the end of the motor neuron evokes liberationof acetyl choline from the vesicles in the nerve synaptic terminals.

- Secreted by neurons in many areas of the brain (in all synapses)

- Has mainly an excitory effect.

- In the peripheral parasympathetic nervous system – inhibitory effect.

- Anticholinesterases – prolong acetyl choline or parasympathetic action

  e.g. Neostigmine used for treatment of myasthenia gravis (achronic progress muscular weakness with atrophy).

Norepinephrine

Chemical mediator at most sympathetic postganglionic nerve endings. Secreted at the ends of presynaptic adrenergic fibers.

- Secreted by neuron.
- Mostly causes inhibition
- Stores in adrenergic fibers
- Some excitation in some areas generally.

Epinerphrine Only in and few neurons
(Release upon stimulates sympathetic N.S. in hyadrenal (adrenergic effect)

- Only of minor importance in the sympathetic nervous system.

Synthesis of epinephrine and norepinephrine from tyrosine.

Dopamine - usually inhibition.

Glycine

Secreted mainly at synapses in the spinal cord. Acts as inhibitory transmitter.

γ-aminobutyric acid (GABA)

Secreted by nerve terminals in the spinal cord, the cerebellum, the basal ganglia and many other areas. Causes inhibition.

Glutamic acid

Secreted by synaptic knobs in some or many of the sensory pathways. Causes excitation.

Substance P

Secreted by pain fibers terminating in spinal cord – causes excitation.

Eukephalins and endorphins

Act as excitatory transmitters to excite another system that in turn inhibits the transmission of pain.

Serotonin

Act as inhibitor of pain pathway in the cord. Helps to control the mood of a person – even to cause sleep.

Electrical Events during Neuronal Excitation

- Resting membrane potential of the neuronal soma
    - 70 millimoles (-90mu in large peripheral nerve fibers and skeletal members)

    ↓ the voltage to a less negative value makes the membrane of the neuron more excitable, whereas increasing the voltage to a more negative value makes the neuro less excitable.

Conc. difference of ions across membrane

Dendrites

Na^+ 142 mEq/ IU mEq/L
pumps

K^+ 4 mEq/L 140 mEq/L
weak pump -70 mU

Cl^- 107 mEq/L 8 mEq/L

(highly permeable membrane to Cl^-. No Cl^- pump)

↓ Cl^- inside due to –70 mU

↑ K^+ inside due to –70 mU

The basic cause of –70 mU resting membrane potential of the neuronal soma is the Na-K^+ pump. More positively charged Na+ is in the than K+ to the itneron ($3Na^+$ for 2 K^+ ions)

Inside large No. of –ve changes:

- Protein ions
- Phosphate
- Others

- Any change in potential in any part of the soma causes a almost exactly equal change in potential at all other points in the soma.

Effect of synaptic excitation in the post synaptic membrane – The excitatory post-synaptic potential

Excited Neuron

Potential must rise to –59 mU to excite the neuron

-70 → -59 : + 11 mU is called excitatory

Postsynaptic potential

Excitatory transmitters act on the membrane excitatory receptor to ↑ the membrane permeability to all ions.

Inhibitory synapses ↑ permeability of post synpatic membrane to K^+ act only.

∴ ↑ K^+ comes out. ↓ to – 75 mU

(Hyperpolarized state)

-75 –70 = -5 diff is called inhibitory postsynaptic potential

LIVER

- Largest organ.
- Most activity metabolically.
- Receives blood from portal vein and in all nutrients except dietary lipid.
- Has many functions:

(A) Metabolic
(B) Excretory
(C) Protective
(D) Storage

(A) Metabolic

(a) CHO

- Glycogenesis – glycogen synthesised and stored in the liver.
- Glycogenolysis – glycogen breakdown during fasting – maintains normal blood glucose level.
- Glucogenesis
- Conversion of fructose and galactose to glucose

(b)
- Lipid metabolism
- Synthesis of:
    - Lipoproteins
    - Phospholipids
    - Cholesterol
    - Endogenous TAG
    - FA synthesis
    - Ketone bodies from acetyl CoA

- Cholesterol – Cholesterol esters
- Cholesterol – bile acids Taurine / Glycine → Bile salts

- Cholecalciferol 25-Hydroxylas 25-hydroxy cholecalciferol

Protein and a.a. metabolism

- Transamination and deamination of a.a.
- Urea synthesis
- Synthesis of many plasma proteins:
    - Carries proteins
    - Coagulation factors:
        - Prothrombin
        - Factor VII, IX, X

(B) Excretory Function

- Excretion of bile pigment (e.g. bilirubin) in cholesterol in bile.
- Several drugs after detoxication.
- NH_3 – urea – excreted in urine via kidney.
- Steroid hormones - after conjugation excreted in urine.

(C) Protective function

- Detoxication of endogenous substances
  e.g.bilirubin, steroid hormones, NH_3
- Detoxication of drugs.
- Detoxication of toxic sub. produced in the large interins:
  - Tyramine
  - Histamine
  - Indole
  - Phenol

(D) Storage

- Glycogen
- Vitamins
  - A
  - D
  - B12
  - B6
  - K
- Iron

Detoxication Mechanisms in Liver

Liver detoxifies several toxic substances e.g.

- Drugs and their metabolites
- Metabolites – (normal)
- Intestinal Toxins

By detoxication reactions:

- Oxidation
- Reduction
- Hydrolysis
- Conjugation
- Methylation

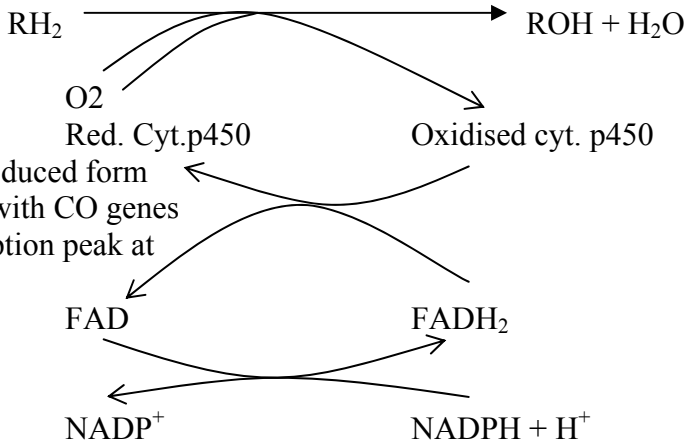
(1) Oxidation:

- Major process for detoxication of drugs and nontoxic drugs is excreted
- 2 types of oxidation
  (a) Microsomal oxidation
  (b) Non microsomal oxidation

(a) Microsomal oxidation

- Microsomal oxidase system called "Mixed function oxidases" – consist of cytochrome p450 (a haemoprotein) + NADPH + FAD and molecular O_2.
  As they reduce mol. O_2 while oxidising the substrate.

- Bring about hydroxylation of the toxic substance a



So called as its reduced form after combining with CO genes and strong absorption peak at 450 nm.

Upon hydroxylation the drugs can be further conjugated with glucuronic acid or sulfate to be made soluble and excrted easily

e.g. Drugs:
- Phenobarbitone
- Morphine

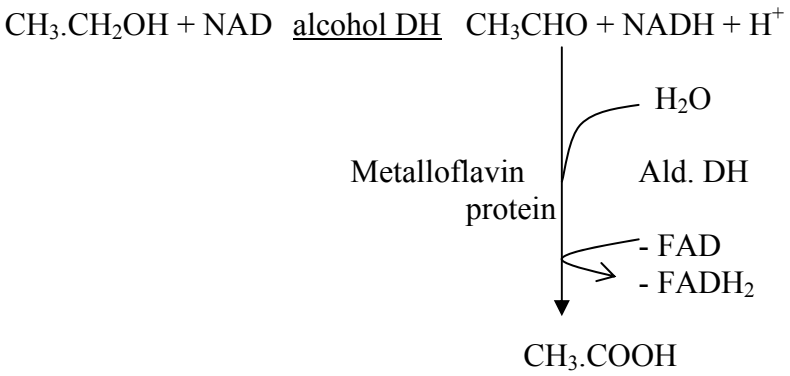
Aniline Hydroxy-methyl benzene

MFO induced by barbiturates and polycyclic hydrocarbons.

(b) Nonmicrosomal oxidation

- In cytoplasm and mitochondria of liver,
- Do not need cyt-p450 kidney and other tissues

e.g.

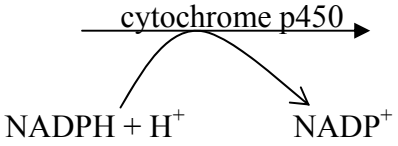


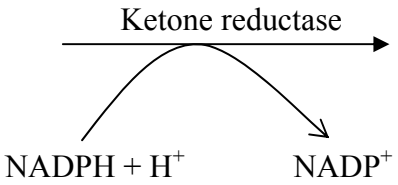
Reduction

- Hepatic microsomal enzymes
- By addition of hydrogen

e.g.

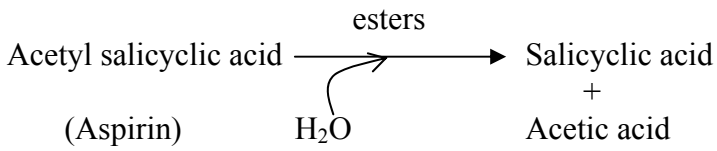
nitrobenzene

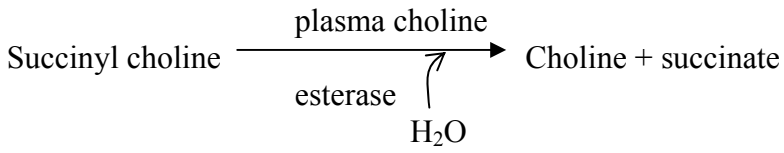


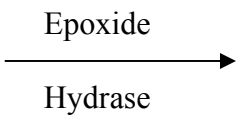


(3) Hydrolysis

- By esterases - present in:
  - Liver
  - Plasma
  - Brain
  - Intestinal mucosa
  - RBC
  - Muscles
- Hydrolysis of esters







4. <u>Conjugation</u>

- Large number of endogenous and exogenous molecules are detoxified by conjugation.

- 4 types of conjugation

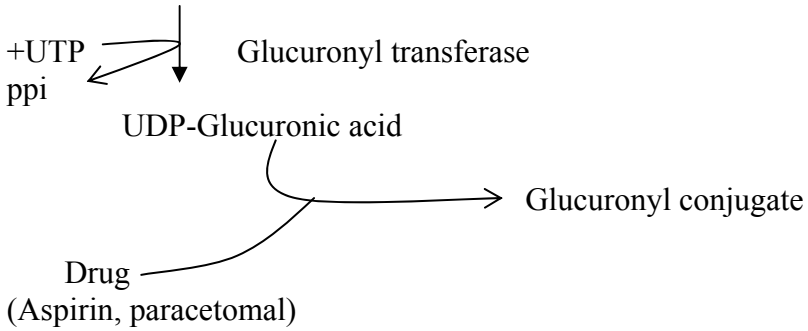
(1) <u>with glucuronic acid</u>

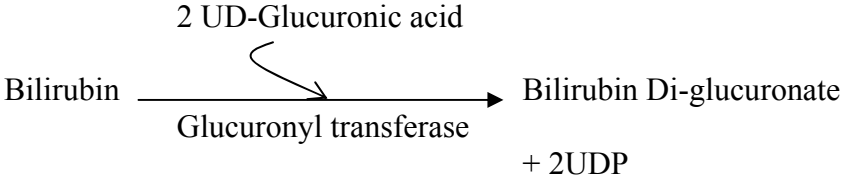
- Hydroxyl (both phenolic and alcoholic)
- Carboxyl
- Sulphydryl
- Amino

<u>Enzyme.</u> UDP-Glucuronyl transferase - present in ER

Donor UDP-Glucuronic acid

G-1-P





(b) Conjugation with acetic acid

e.g. Sulphonamides

COASH
Acetic acid → Acetyl CoA
Thokinase
ATP AMP

Acetyl sulphonamides

Sulphonamide
N-Acetyl transferase

(c) Conjugation with Glycine

e.g. Benzoic acid

(Benzoic acid) → Clycine → Hippuric acid

Benzoyl CoA

Bile acid + glycine ⟶ Bile salts

Bile acid + Taurine ⟶ Bile salts

(d) Sulphate

Sulphate donor → 3'-phosphoadenosine-5'-phosphosulfate (pAPS)

ROH + PAPS ⟶ RO.SO3H + PAP
Sulfo-transferase

Phenol → Phenyl sulphuric acid

Indole O_2 → Indoxyl PAPS → Indoxyl sulphuric acid

(Potassium indo-sulphate) Indican

(e) Glutathione conjugation

- Glutathione transferase

Substates Thioesters
Glutathione Mercepturic acid

(Alkyl and arylhalides
epoxides and alkenes)

(f) Glutamine conjugation

Glu transferase

Phe phenylacetic acid + glutamine phenacetyl glutamine

LIVER FUNCTION TESTS

Biochemical Tests

- Detect changes in the function and structure of the liver.

(A) Common liver FT:
- Qualitative assessment of bile pigment level
  - Stool
  - Urine
  - Blood
- Plasma enzyme level
- Plasma protein level

(B) Other LFT

(1) Bile pigment level in urine stool and blood

(1) Bile pigment in urine

- Bilirubin:
  - usually no bilirubin
  - ↑ conj. inhepatic and posthepatic jaundice
  - None in prehepatic
- Urobilinogen:
  - Small amount normally
  - Prehepatic - ↑ urobilinogen
  - Hepatic - ↑ urobilinogen
  - Post hepatic - ↓ urobilinogen

(2) Changes in colour of stool

- Prehepatic I - Dark color (↑ urobilinogen)
  ↓
  urobilin
- hepatic I - pale - (↓ urobilinogen)
- posthepatic I - clay coloured (no urobilinogen)

(3) Bile pigments in plasma

Prehepatic I - Plasma bilirubin - Slightly ↑ (unconjugate)

Hepatic - Moderately ↑↑ - > ½ conjugated

Posthepatic - ↑↑↑- Almost all conjugated.

(2) Tests that measure plasma enzyme levels:

- Transaminases:
  - AST (Aspartate aminotransferase)
  - ALT (Alanine aminotransferase)

Liver Rich Source - Liver cell damage - Release in AST and ALT

Prehepatic Jaudice - normal AST and ALT
Hepatic Jaundice - Moderate to marked ↑
Posthepatic Jaundice - Normal or moderately ↑

- ALP
  - Synthesised in liver.
  - Secreted in bile
  - ↑ in obstructive both intrahepatic and extrahepatic
  - Prehepatic jaundice - ALP normal
  - Hepatic jaundice - ALP moderately ↑
  - Posthepatic jaundice - ↑↑ ALP

- γ-GT - Similar to those of ALP.

  ↑ in mild liver disease more than the ALT, AST and ALT

↑ in mild liver disease more than the ALT, AST and ALT

(3) Tests to measure plasma protein levels

- Albumin:
  - Synthesised in liver
  - Plasma level - impaired synthetic function

Prehepatic	-	Normal Alb.
Heptatic	-	↓
Posthepatic	-	Normal and ↑ slightly

- γ- Globulin: ↑ chronic liver disease.
  This is due to by-passing of the liver by intestinal toxins.

Prehepatic	-	normal γ-globulin
Hepatic	-	Slightly to markedly ↑
Posthepatic	-	Slightly ↑

(B) Other LFT

Other plasma E

5'-nucleotidase ↑ in liver disease
(ALP ↑ in both liver and bone disease).

Other plasma proteins

1. Alpha fetoproteins:
   - Synthesis in normal fetal liver
   - ↓ syn. after birth
   - ↑ hepatoma
2. Clotthing factors - synthesised in the liver.
   - Prothrombin time - assess plasma level of clotting factor II, V, VII and X.
     ↓ C.F. in liver disease
     ∴ ↑ P.T. in hepatic and posthepatic jaundice
     ∴ clotting becomes slower than normal.
3. Arterial blood ammonia - ↑ in liver failure.
4. CSF glutamine - ↑ chronic liver failure.
   ↑ NH_3 and α-ketogluterate - glutamine
5. Plasma bile acids - synthesised from cholesterol in liver.

Hepatic and posthepatic jaundice - ↑ due to ↓ secretion into the bile.

6. Bromosulphthalein Excretion Test - Dye

- Tests the ability to excrete BSP after conjugation with glutathione (in bile)

- i.v. – Blood taken 45 min. later – Determine % of Dye retained.

  Normally < 5% retained.

  Severe liver disease - > 40% retained.

  Useful for – congenital liver disease (Dubin-Johnson Syndrome)
  ↓
  Slight jaundice

HEPATIC COME

- Coma due to severe liver disease.

- Biochemical complications:

  (a) *NH_3 accumulation.
  In Brain α-keto Glu + NH_3 - Gln
  (Brain deprived of energy)

  (b) *Tyramine and histamine accumulation
  - Produced in large intestine under bacterial effect
  - Detoxified in liver
  - ↑ - Interfere with normal neurotransmission in brain.

  (c) Other toxins e.g. mercaptans and octopamine

(S con from met)	(From ↑ Tyr)
↓	↓
excreted in breath (Feotor hepaticus small)	False neurotransmitter inbrain and Interfere withneurotransmission

(d) *GABA

Normally ↓ GABA
GABA → inhibitory neurotransmitter in brain
↑ interferes with normal neurotransmission
↑ is due to ↑ Glu from NH_3

Excretory Functions

- Bile formation and excretion
- Bilirubin conjugation
- Cholesterol
- Bile salts
- Phospho
- Secretion in the bile of products from liver parenchymal cell
- Excretion of substances withdrawn from the blood by hepatic activity e.g. Heavy metals, dys such as bone sulphalein and alkali phosphatase.

Bile - in liver

(a) Bile acids - (primary bile cholic and chinodeoxycholiacid acids)

Deoxycholic and lithocholic acid
(Secondary bile acid) - intestinal bacteria
and their salts - with glycine and taurine

Bile - common bile duct to the directly into the duodem or stored and conc. in the gall bladder.

Bile acids needed for enubification of dietary lipid needed for digestion and absorption of dietary fat.

Secretion of bile from the liver and empting of the gall bladder are under normal control. Hepatocrinin stimulates bile secretion by liver.
and cholecystidin - causes gall bladder to emply
15-30 g/day bile
~ 300 mg/day is lost in feces.

STORAGE FUNCTIONS

Vit A

Liver can store sufficient vit. A to last for months or even years. Less than 1 mg/day.

In liver carotine vit A

Vit D ~ 20 ug/day

This vit. can be stored in sufficient amounts in the liver for a single dose to suffice for some weeks.

Vit E

Vit. R

Fe

The storage form of iron, ferritin, is good in the liver (~700 mg) intestine, spleen and bone marrow.Excessive Fe absorption in toxic for all tissues – may cause cirrhosis, diabetes and pancreatic fibro

Storage of Glycogen

Nitrogen Excretion

NH_4, CO_2 and O_2 are the three gaseous substrate of the body. Virually, the sole function of oxygen is to combine with the hydrogen removed from the substrate during catabolic reactions to yield water that may leave the body by the lungs, skinor kidney. The other two gases are concerned in both catabolic and anabolic reactions according to the needs of the body. CO_2 leaves the body by the lungs and the kidney, whereas NH4 leaves only by the kidney. Both CO_2 and NH_4 are closely monitored excess of either may have toxic effects on the whole body.

The conc. of NH_4 in the tissues varies. In heart muscle it is 0.2 mM; in abdominal muscle and kidney – 0.9 mM; in the brain and thigh muscle – 0.3 mM and in liver 0.7 mM. The conc. of NH_4 in blood, except, partial blood is about 0.05 mM.

Within the cells of tissues other than the liver the NH_4 can be removed by two reactions:

$$\alpha\text{-ketoglutarate} + NADH_4 + H+ + NH_4 \xrightarrow[\text{dehydrogenase}]{\text{glutamine}} \text{glutamate} + NAD^+ + H_2O$$

$$Glu + NH3 + ATP \xrightarrow[\text{Synthetase}]{\text{glutamine}} \text{glutamine} + ADP + Pi$$

The Glu can transfer its ammino group to either keto acids to yield a different amino acid.

$$Glu + Pyr \rightleftharpoons ala + \alpha\text{-keto Gln}$$

Substances such as pyr that are in relatively plentiful suply can ∴ be used as depository for excess NH_4 group. NH_3 is ∴transported as amino acid having a total conc. of about 3-4 mM: Glu, Glu and Ala are the most plentiful. Gln and Ala can penetrate into liver most easily.

The liver receives NH_4 by two main routes, from the portal blood as free NH_3 and a.a. and from the systemic blood as a.a. The amount of free NH_3 formed by bacterial action in the gut and of a.a. in the portal blood depends on the diet. In the normal man the portal blood contains about 0.18 mM NH_3 is the form of NH4+ (98%). The venous outflow from the liver contains 0.6 mM NH_3. Within the liver NH_3 can arise from the action of glutaminase.

$$Gln + H_2O \rightarrow Gln + NH_3$$

or from AMP by the actionof adenylate deaminase.

$$Asp + GTP + IMP \longrightarrow \text{adenyl succinate} + GDP + P$$

$$AMP + H_2O \longrightarrow IMP + NH_3$$

NH_3 can also arise from Gln catalysed by Gln-dehydrogenase. The above two reactions are irreversible the latter reaction (Gln) is reversible and is equilibrum with most other a.a.s. of transamination reactions. Thus in times of ammonia overloading it will be removed from the system first forming Gln and thence by transamination forming Ala from Pyr and lactate that are always present. The presence of Gln – dehydrogenase and the transaminase system thus results in an overall buffering of the NH_4+ conc. within the liver – 0.7 mM. This is the Km for NH_3 of carbamyl (p) synthetase. Thus this enzyme starts the urea production and also contributes towards buffering the NH_3 conc.

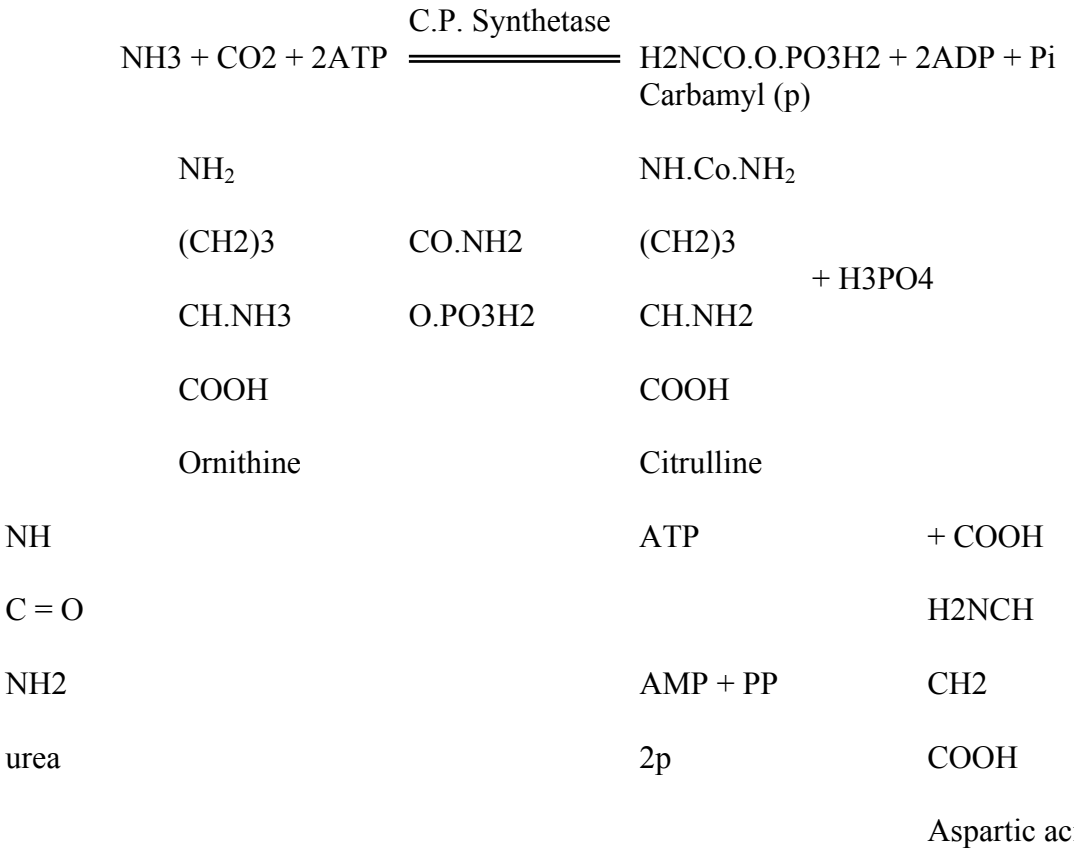
In the formation of urea the two ntirogens arise from two diff. sources:

- NH_3
- Aspartate

The amounts of these two nitrogen's donors must be kept in balance. With excess of free NH_3 gut will be formed which will transaminate the available oxiacet to form the necessary Asp. The α-keto Gln liberated from the transamination may be either reanimated or oxidized to provide ox. Ac for the production of more Asp. Thus the production of removal of NH_3 is automatically adjusted to the metabolic needs of the cell.

The Urea Cycle

Most of the ammonia excreted by the kidney is in the form of urea; synthesized primarily in the liver. The daily elimination of urea is about 25g, nearly 90% of the nitrogenous excretion. Sincre urea is formed in the liver, hepatectomy prevents its production and causes a constantly mounting level of blood ammonia.



Hydroxylation

Hepatic endoplasmic reticulum - capable of hydroxylation uses NADPH + H^+ as a reductet.

Sub — OH – Substrate

O_2 — H_2O

Red. Cyt. p450 — Oxi. Cyt. p450

Red. Fe Protein — Oxi Fe protein

Flow protein reduction

Ox. F.P.

$NADP^+$

$NADPH + H^+$

LIVER FUNCTIONS

1. Metabolic Functions:
    - Involving carbohydrate, protein, fat metabolism.
2. Detoxication and protective functions:
    - Conversion of ammonia to urea
    - Formation of bilirubin glucuromides
    - Drug detoxication
    - Steroid inactivation, etc.
3. Excretory Functions:
    - Formation of bile and excretion of bilirubin.
    - Formation of bile salts.
    - Excretion of bromosulfalein and other foreign compounds

4. Storage functions:

    - Storage of glycogen
    - Storage of Iron
    - Storage of Several Vitamins (A, D, B12)
    - Storage of Minerals

5. Hematological Functions:

    - Hematopoises during embryonic development
    - Formation of clotting factors
    - Synthesis of plasma proteins

6. Grulatory Functions:

    - Participates in blood storage
    - Intermediary between portal and systemic blood circulation
    - Reticulo-endothelial activates of Kupffer cells

LIVER METABOLISM

- Liver actively metabolises carbohydrate, fats and proteins.

- Fats are the main source of energy.

- Amino acids are also used for energy production.

- Relatively little glucose is used to provide energy.

- Excess glucose is stored as glycogen.

- OR/AND is converted to cholesterol and tri-acyl-glycerides.

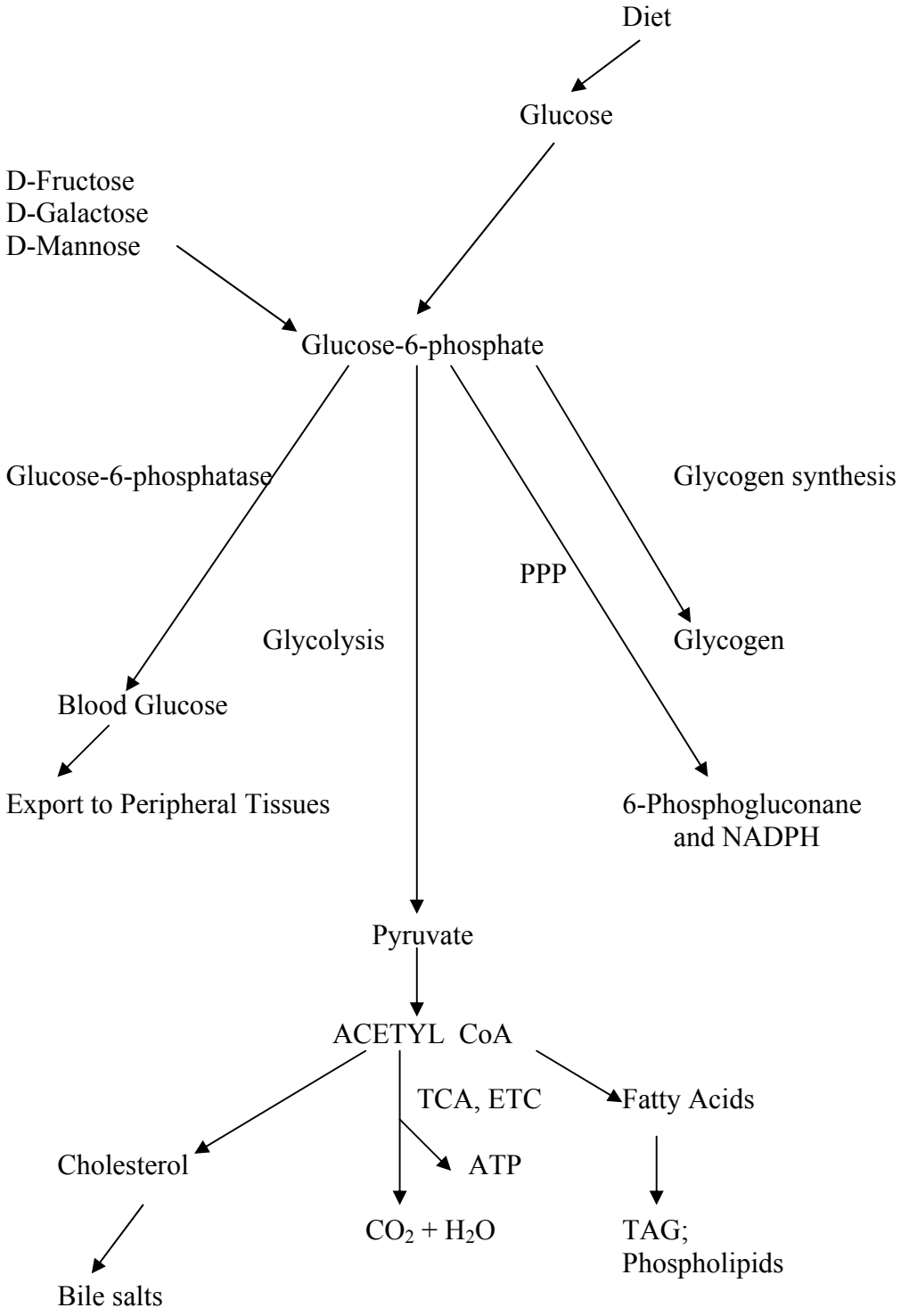
- Synthesis of glucose from non-carbohydrates substances (takes place by the pathway of gluconeogenesis.

- Ketone bodies are synthesised but not metabolized by the liver.

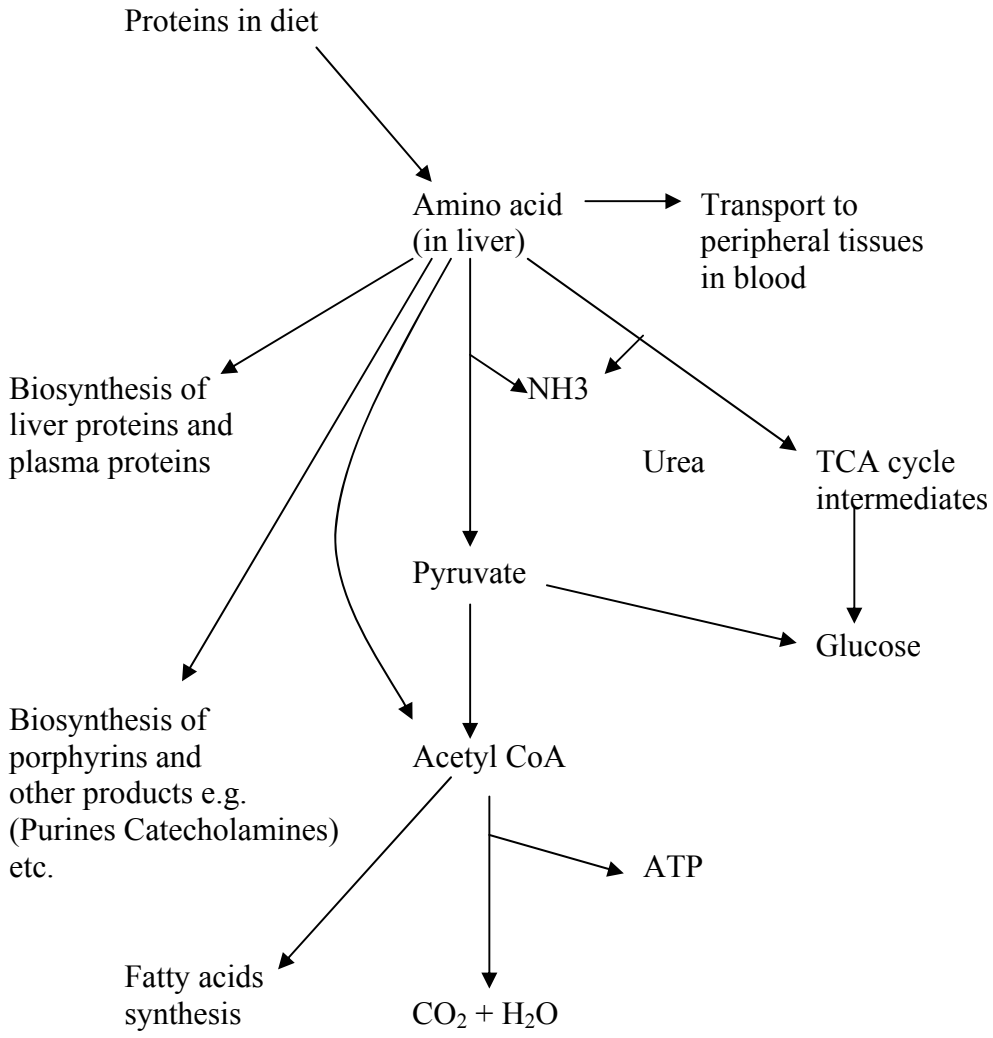
- Protein turnover rate is high.

- The liver helps to maintain the blood glucose level constant.

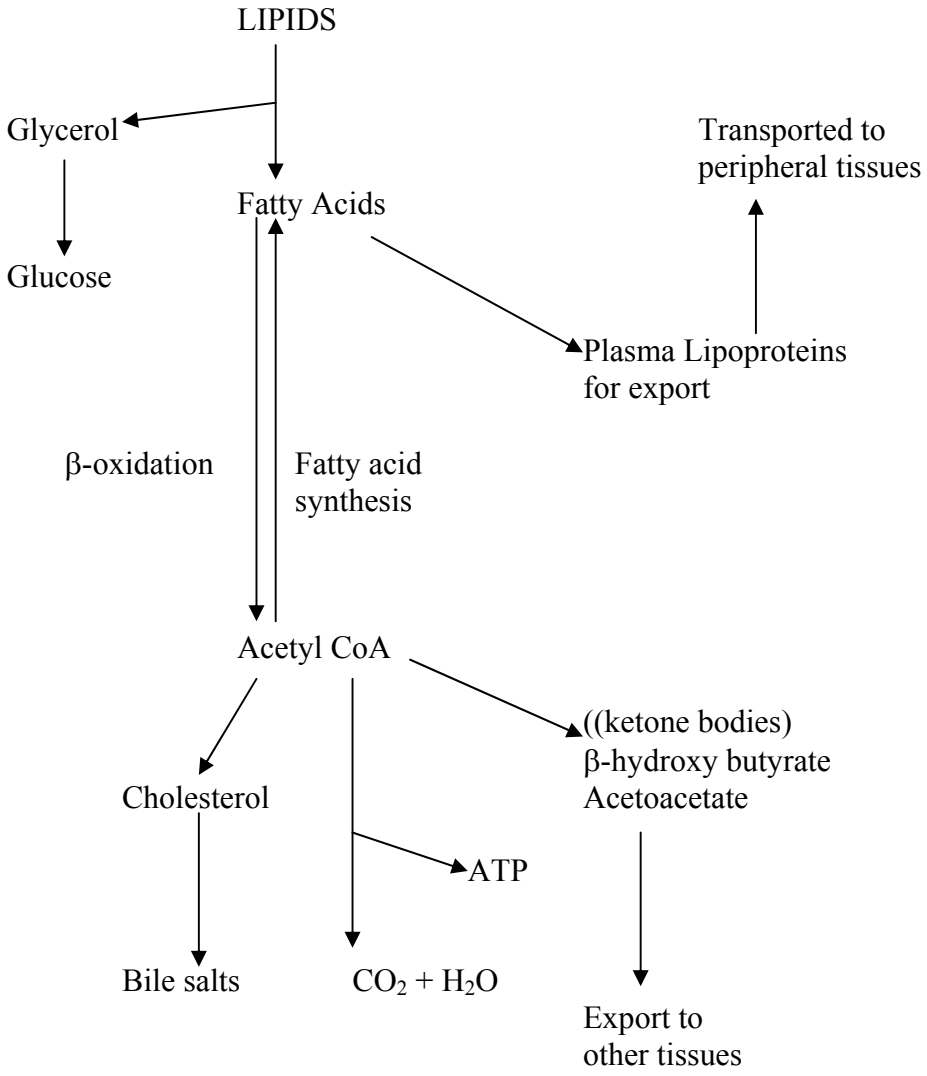
(i) **Carbohydrate Metabolism**



(ii) **Amino Acid Metabolism**



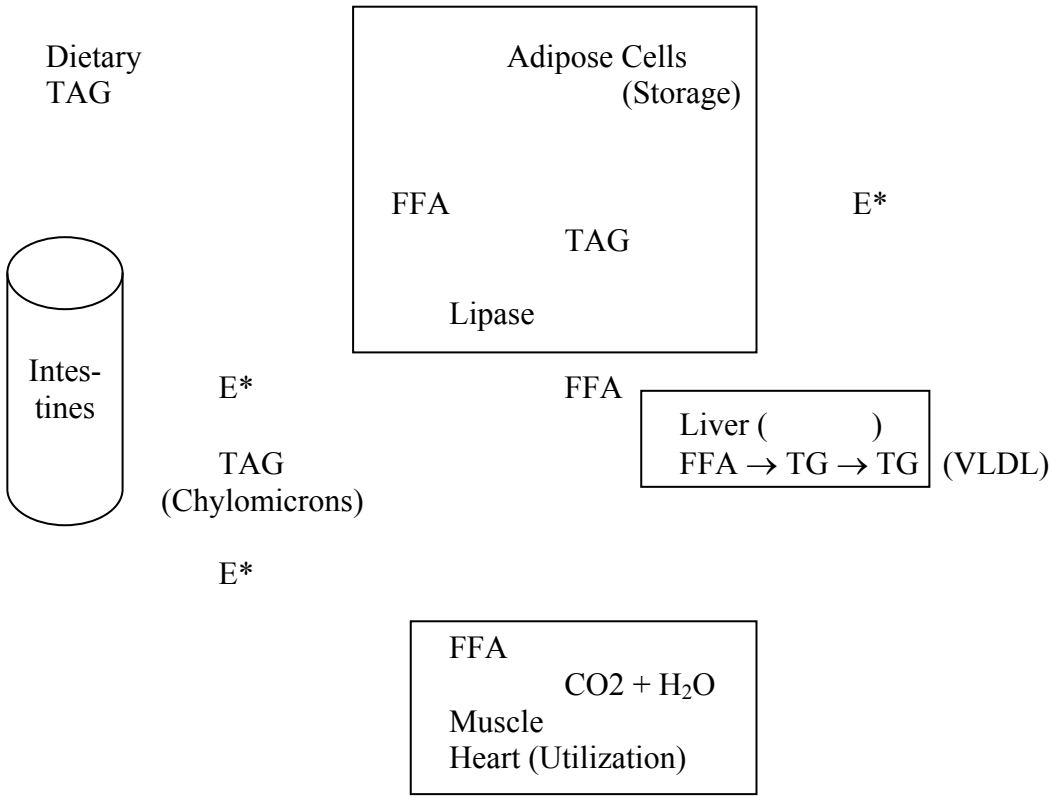
(iii) **Lipid Metabolism**



Muscle Metabolism

- Skeletal muscles utilize about 30% of the resting oxygen consumption.
- Increase in muscular activity increases oxygen consumption.
- Normally, the main fuel are fatty acids, which are catabolized to give acetyl CoA.
- During muscular activity there is a large increase in glucose consumption.
- Glucose forms pyruvate by glycolysis.
- Pyruvate forms lactate.
- Lactate is converted to glucose in the liver – Cori cycle.
- Fatty acid and triacyl Glyceride synthesis occurs in the muscles.
- The protein turnover rate is high.

CIRCULATION OF LIPIDS



E* = Clearing factor – Lipase

E**INTEGRATIONBETWEEN LIVER, BRAIN, MUSCLE AND ADIPOSE TISSUE**

HEART - METABOLISM

- Normally the major fuel for heart are free fatty acids (~ 70% of the total consumed fuel)

- Some ketone bodies, blood glucose and lactate are also used as fuel.

- Very little lactate is formed from pyruate.

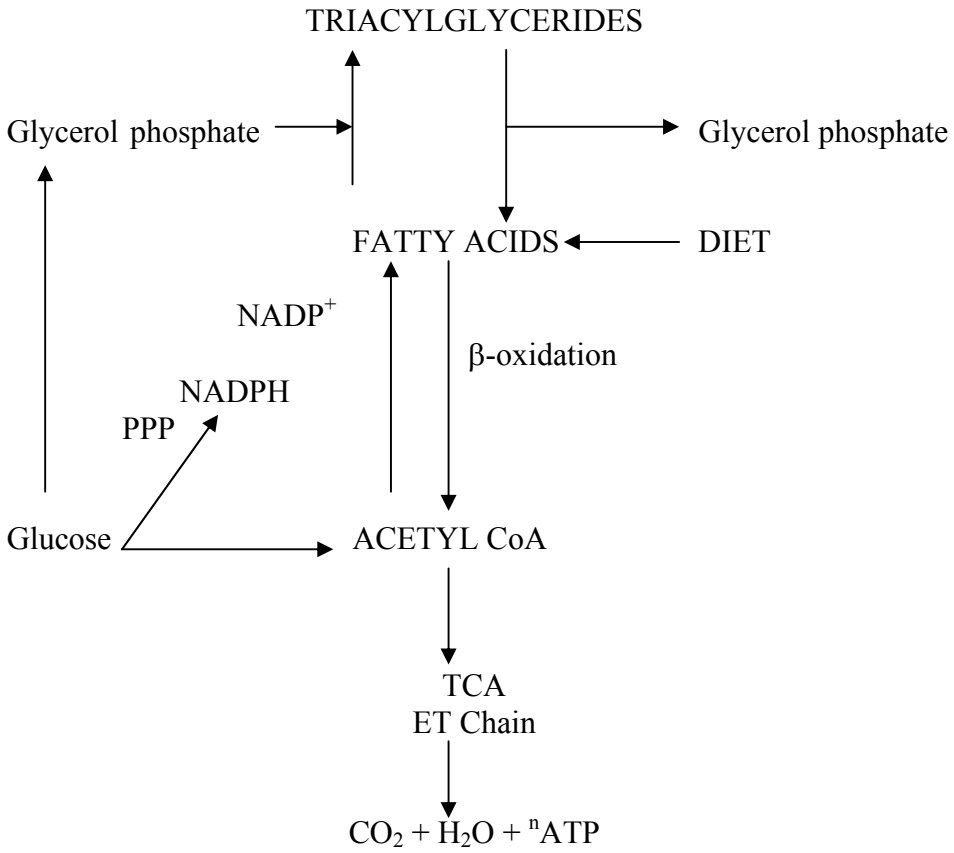
- Imposition of a work load on the heart leads to (a) increase in the oxygen consumption, (b) increase utilization of glucose (~ 82% of total consumed fuel) for a few seconds.

  (b) Increase in the amount of lactate formed from pyruvate.

- 2 minutes after the imposition of a work load the heart adjusts its metabolism again to oxidation of fatty acids and decrease in the rate of glucose utilization.

- Proteins of heart have a high turnover rate.

ADIPOSE TISSUE - METABOLISM



ADIPOSE TISSUE – METABOLISM

1. The main fuels used by adipose tissue are glucose and fatty acids.
2. Glucised is used to synthesise triacyl glycerides (TAG) as it can provide acetyl CoA. NADPH acids are stored as tri-acyl glycerides.
3. Fatty acids are stored as tri-acyl glycerides.
4. Mobilization of fatty acids is brought about by hormone-sensitive lipase.
5. Glucose is not stored as glycogen.

Kidney

Very ↑ rate of respiratory met.
Metabolic flexibility.

Utilizes as fuel:

- Blood glucose-small a mol. After feeding 2-6% of O_2 consumption.
  Glycolysin.

- FFA (palpitation): 1st 60-80% fuel of impact kidney.
- KB in fasting, starvating, DM
- a.a. (G/n) – lactate – 2nd most imp. fuel
- Cirate
- Glycol

ATP by aerobic oxidationof substrate glycolysin
~ 4% of ATP major use of ATP – reabsorption of NaCl by kidney tube.

- Preference of fuel depends on availability in blood plasma.

  ↑ palmitate – inhibits utilization of lactate for energy

- Does not inhibit uptake of lactate
  Lactate gluconeogene Glucose

- Also uses 2nd – 3/4th energy for urine formation

- Glomeruli filtration (in glomeruli in cortex)

  Filter all solutes of blood plasma except lipoproteins and proteins

- Reabsorption in passing through renal tubules – Na^+, Cl^-, glucose, a.a. water reabsorption

∴ More concentrated filtrate
(1 ml of urine formed from 50-100 glomerular filtrate)

Kidney Cortex and kidney medulla differ in metabolism

Cortex: - ↑ rate of O_2 consumption.
↑ TCA and ETC
Respiratory constant of 0.75
Synthesis of glucose occur in fasting
FA principal glue
Use palmatate, lactate, KB and glocuse
Some KB formation

Medulla:
- ↑ conc. of E of glycolysis
- ↓ TCA and ET enzymes
- ↓ rate of O_2 consumption
- ↓ rate energy requirements
- Energy mainly from glycolysis
- Source of glucose – plasma glucose and glucose synthesis in cortex in fasting

Gluconeogenesis:

- In kidney cortex - more rapid glucose synthesis/unit wt than in liver, but does not provide blood glucose.

- Used by medulla as final.
  ↑ gluconeogenesis in fasting. Activated by epinephrine and glucogon via AMP.

- During fasting cortex gets energy from FA and KB for gluconeogenesis.

- ↑ rate of glyconeogenesis by acidosis.
  Induction of phosphoenol pyruvate carboxy kinase.

NH3 production in kidney

↑ NH_3 production and excretion – Acid base balance
e.g. in control of metabolic acidosis.

Phosphate dependent – Glutaminase
$\longrightarrow$ Glu + NH3
(Mitochondrial matrix and inner membrane)

Special transport carrier into mitochols

Kidney tubular transport mechanism

Kidney -richest source of Na^+, K^+ - stimulated ATPase

↑ Conc. in thick ascending loop of Hence and proximal tubultes

$$3\,Na^+ + 2K^+ + ATP + H2O \xrightarrow{ATPase}$$

(Inside) (Outside)

$$3Na^+ + 2K^+ + Pi$$

(Outside) (Inside)

$ADP + H^+$

Function of this E is the active transport of K^+ and Na^+ inside and outside of the cell respectively.

- Ion movement occurs mainly in the ascending loop of Henle. Reabsorbs NaCl.
- Transport of D-glucose and a.a. in proximal region of the nephron) from the glomerular filtration into the blood is energy dependent, saturable and is stimulated by Na^+.

Urine	24 hr. urine, vol. 1,200 ml	
V. low glucose	0.02 as it is reabsored	< 0.02
*Ammonia	0.8	100
A.A.	0.5	1.0
*Urea	25	70
*Creatine	1.5	70
*Uric acid	0.7	20
*H^+ pH	5-8	upto 300
Reabsorbed Na^+	3.0	1.0
K_+	1.7	1.5
Ca^{++}	0.2	5
Mg^{++}	0.15	2
Cl^-	6.3	1.5

Phosphtase	1.2	25
Sulfate	1.4	50
Bicarbonate	0-3	0-2

The inward directed Na+ gradient so generated is used for the active transport of both glucsoe and a.a.