BP-204T.PATHOPHYSIOLOGY (Theory)

UNIT- ONE

Prepared By,

Ms. ARPITA CHOUDHARY

Assistant Professor

Faculty of Pharmaceutical Sciences,

Rama University, Kanpur (U.P)

UNIT-ONE **10 Hours**

- **Basic principles of Cell injury and Adaptation:**
  Introduction, definition, Homeostasis, Components and types of feedback systems, Causes of cellular injury, Pathogenesis(Cell membrane damage, Mitochondrial damage, Ribosomal damage, Nuclear damage), Morphology of cell injury(Adaptive changes)- Atrophy, Hypertrophy, Hyperplasia, Metaplasia, Dysplasia, Intracellular accumulation, Calcification, Acidosis, Electrolyte imbalance.
- **Basic mechanism involved in the process of inflammation and repair:**
  Introduction, Clinical signs of inflammation, Different types of Inflammation, Mechanism of Inflammation- Alteration in vascular permeability and blood flow, mediators of inflammation, Basic principles of wound healing in the skin.

INTRODUCTION

- For understanding diseases, we need to focus on the study of abnormalities in structure and function of cells in diseased state. This is because most forms of diseases begin with cell injury. Cell injury can occur because of an adverse stimulus which disrupts the normal homeostasis of affected cells.

CELL INJURY

- Cell injury is defined as the effect of variety of stress(due to causative agents), a cell encounters resulting in changes in its internal and external environment.
- Cell injury depends upon two variables.
  (i)Host factors (i.e. the type of cell and tissue involved)
  (ii) Factors pertaining to injurious agent (i.e. extent and type of cell injury)

TYPES OF CELL INJURY

- **REVERSIBLE CELL INJURY –** When the stress is mild to moderate, injured cell may recover. This is known as reversible cell injury.

- **IRREVERSIBLE CELL INJURY –** If stimulus is severe or stimulus persist, cell reaches the point of no return and cell death occurs. This is known as irreversible cell injury.
- Reversible or irreversible injury depends on nature of the cells, cellular metabolism, blood supply and nutritional status of the cell.

CAUSES OF CELL INJURY (ETIOLOGY) :

- **A cell may be injured by two ways -**

  A. Genetic Causes.

  B. Acquired Causes

A. GENETIC CAUSES :

Genetic causes includes some disorders and abnormalities caused due to some genetic defect. They are as follows:

1..**Mendelian disorder–**A type of genetic disorder resulting due to alteration in one gene (or alteration in genome).

2.**Chromosomal abnormalities -** like Polyploidy, Aneuploidy .

3. **Sickle cell anemia-** inherited group of disorders in which RBC's changes into sickle shape, dies early leaving shortage of healthy RBC and can block blood flow.

4.**Down's Syndrome -**Genetic disorder caused when abnormal cell division results in extra genetic material from chromosome no. 21.

B. <u>ACQUIRED CAUSES :</u>

1. **Hypoxia:** It is an extremely important and common cause for cell injury and cell death. Loss of blood supply (ischemia) is the common cause of hypoxia. Hypoxia also occurs from cardio respiratory failure, loss of oxygen carrying capacity of blood (anemia, C, O poisoning etc.). Hypoxia impairs the aerobic oxidative respiration.

2. **Physical agents-** extreme temperature, Radiation, Rapid Change in atmospheric pressure.

3. **Chemical agents-**cyanide poisoning ,arsenic poisoning, environmental pollutant, insecticides, pesticides, alcohol and narcotic drugs.

4. **Infectious agents -** injuries caused by microbes, infection caused by bacteria, virus fungi, protozoa, parasites etc.

5. **Immunologic reactions** -hypersensitivity reaction.

6. **Nutritional Imbalance –** Deficiency or excess of nutrition like marasmus (deficiency of proteins), deficiency of minerals(anemia)

7. **Psychological factors –** Drug addiction, alcoholism, smoking.

<u>Cell death</u>:

- It is the ultimate result of cell injury.
- Patterns of cell death are-

  (i)Necrosis

  (ii)Apoptosis

<u>NECROSIS-</u> A form of cell injury which results in premature death of cells in livingtissue. It is caused by infection, trauma which result in unregulated digestion of cell components.

<u>APOPTOSIS -</u> More regulated form of cell death, designed for normal elimination of unwanted cells, during various physiologic processes It's a pathway of cell death that is induced by tightly regulated suicide program. Cells activate enzymes capable of

degrading the cell's own nuclear DNA and nuclear and cytoplasmic proteins. The fragments of apoptotic cells then break off. The plasma membrane of the apoptotic cell remains intact, but the membrane is altered.

PATHOGENESIS (MECHANISM) CELL INJURY

- To understand the biochemical structural and functional changes that occurin

  cells, tissues and organs variety of techniques being used by the pathologist.

- They identify changes in the microscopic appearance(morphology) of cells and tissues and also the alteration in body fluids.

(a)Damage to plasma membrane-

- Due to lack of ATP, generation of phospholipids from the cellular fatty acids is interrupted.
- Phospholipids are required for continious repair of membranes.
- This results in damage to membrane pumps operation for regulation of sodium-potassium and calcium.

(b)Mitochondrial Damage-

- Due to excessive influx of calcium ions, excess intracellular calcium collects in the mitochondria and interrupts its functioning.
- Mitochondrial damage can be seen in the form of vacuoles in the mitochondria and deposits of amorphous calcium salts

(c) Ribosomal Damage-

- As a result of continued hypoxia, ribosomes gets detached from rough endoplasmic reticulum. This leads to disappearance of ribosomes in the cytoplasm. Functions of ribosomes gets interrupted.

(d)Nuclear Damage-

- Due to low oxygen supply to the cell, aerobic respiration by mitochondria fails, due to which energy requirement by the cell is not fulfilled.
- This causes rapid depletion of glycogen and accumulation of lactic acid. As a result intracellular pH is lowered. Clumping of nuclear chromatin takes place.

CELLULAR ADAPTATION -

Cellular adaptation is a reversible adjustment to environmental condition. That includes changes in cell function, morphology or both. When stimulus is reversed cell revert to their normal state. When limit of adaptive response to stimulus are exceeded; adaptation is not possible and lead to cell injury.

MORPHOLOGY OF CELL INJURY(or CELLULAR ADAPTATION)

Pathologic adaptations are responses to stress that allow cells to modulate (modify) their structure and functions so as to escape from injury.

The main adaptive responses are -

A. HYPERTROPHY- It is an increase in the size of cells resulting in increase in the size of the organ. It can be caused by:

- Hormonal stimulation- cells depends on hormonal support.
- Increased functional demand- Increased functional demand stresses cells and causes them to enlarge and increase their activity. For example, a heart under a constant strain of high blood pressure increases in size because the individual cardiac muscle cells increase in size.

B.

B. HYPERPLASIA- It is the enlargement of a tissue or organ owing to an increase in the .It is Hormonal stimulation. For example, the increase of oestrogen in female puberty causes an increase in the number of endometrial cells.

- Increased functional demand. Example- low atmospheric oxygen stimulates bone marrow production of RBC to carry oxygen.
- Chronic stress or injury.

C. METAPLASIA –

- Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.
- In this type of cellular adaptation, cell sensitive to a particular stress are replaced by another cell types better able to withstand the adverse environment(more durable and related)
- Example – Conversion of fibrous tissue into bone,

D. AUTOPHAGY –

- Autophagy refers to lysosomal digestion of cells own components and is contrasted with heterophagy in which a cell (usually a macrophage) ingests substances from the outside for intracellular destruction.
- Example. Degradation of excess peroxisomes.

HOMEOSTASIS

- Homeostasis is the ability of organism to maintain a relative stable environment inside the body(steady state), when the external environment is changed.
- This is also known as Dynamic state of equilibrium or balance.
- The body is said to be in homeostasis when its cellular needs are adequately met and functional activities are occuring smoothly.

- Every organ system plays a role in maintaining the internal environment.

FEEDBACK SYSTEM

- A feedback mechanism is a physiological regulatory system that either returns the body to a normal internal state(homeostasis) or less commonly brings an internal system further away from homeostasis.
- These act via nerve pathways(neurotransmitters) or via chemicals such as hormones to cause a stimulatory or inhibitory effect.

COMPONENTS OF FEEDBACK SYSTEM

Feedback system consists of three parts –

1. Receptors. It monitors changes in a controlled condition. It also receives information and sends this do the control centre via sensory receptors.
2. Integrated centre. It analyzethe incoming information and send reply via motor receptors.
3. Effectors. They are the cell/ organ that responds according to output command of the control centre via motor receptor.

TYPES OF FEEDBACK SYSTEM

There are two types of feedback system :

(a)Negative Feedback-

- When the response of effectors opposes the original stimulus it is known as negative feedback.
- It always maintains homeostasis/restores homeostasis.
- Examples- Brain controls normal body temperature homeostasis by negative feedback, Hormonal control, Control of blood glucose level , pH control etc.

(b)Positive Feedback –

- The effectors adds up to the initial stimulus instead of negating it, speeding up the process.
- This amplifies the original action.
- It sometimes break down the homeostasis of the system.
- Examples – Blood clotting, Digestion, Labour and child birth.

Intracellular Accumulations

- Under some circumstances cells may accumulate abnormal amounts of various substances, which may be harmless or associated with varying degrees of injury The substance may be located in the cytoplasm, within organelles (typically lysosomes), or in the nucleus, and it may be synthesized by the affected cells or may be produced elsewhere.

- There are three main pathways of abnormal intracellular accumulations:

- A normal substance is produced at a normal or an increased rate, but the metabolic rate is inadequate to remove it. An example of this type of process is fatty change in the liver.

- A normal or an abnormal endogenous substance accumulates because of genetic defects in its folding, packaging, transport, or secretion. Mutations that cause defective folding and transport may lead to accumulation of proteins (e.g., al-antitrypsin deficiency).

- An inherited defect in an enzyme may result in failure to degrade a metabolite. The resulting disorders are called storage diseases.

- An abnormal exogenous substance is deposited and accumulates because the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulations of carbon or silica particles are examples of this type of alteration.

Pathologic calcification

- It is a common process in a wide variety of disease states; it implies the abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals. When the deposition occurs in dead or dying tissues, it is called dystrophic calcification; it occurs in the absence of calcium metabolic derangements (i.e., with normal serum levels of calcium).
- The deposition of calcium salts in normal tissues is known as metastatic calcification and almost always reflects some derangement in calcium metabolism (hypercalcaemia).It should be noted that while hypercalcaemia is not a prerequisite for dystrophic calcification, it can exacerbate it.

Dystrophic calcification: deposition of calcium at sites of cell injury and necrosis.

Metastatic Calcification: deposition of calcium in normal tissues caused by hypercalcaemia.

Abnormal Intracellular Deposition

Abnormal deposits of materials in cells and tissues are the result of excessive intake or defective transport or catabolism.

- **Depositions of lipids**

- **Fatty change:** accumulation of free triglycerides in cells, resulting from excessive intake or defective transport (often because of defects in synthesis of transport proteins); manifestation of reversible cell injury.

- **Cholesterol deposition:** result of defective catabolism and excessive intake; in macrophages and smooth muscle cells of vessel walls in atherosclerosis.

- **Deposition of proteins:** reabsorbed proteins in kidney tubules;
- **Deposition of glycogen:** in macrophages of patients with defects in lysosomal enzymes that break down glycogen (glycogen storage diseases).

- **Deposition of pigments**: typically, indigestible pigments, such as carbon, lipofuscin (breakdown product of lipid peroxidation), iron (usually due to overload, as in haemosiderosis).

Acidosis is a process causing increased acidity in the blood and other body tissues (i.e., an increase in hydrogen ion concentration). If not further qualified, it usually refers to acidity of the blood plasma.

ELECTROLYTE IMBALANCE

- Normally, concentration of electrolytes within the cell and in the plasma is different. Intra- cellular compartment has higher concentration of potassium, calcium, magnesium and phosphate ions than the blood, while extracellular fluid (including serum) has higher concentration of sodium, chloride, and bicarbonate ions.
- In case of electrolyte homeostasis, the concentration of electrolytes in both these compartments should be within normal limits.
- Normal serum levels of electrolytes are maintained in the body by a careful balance of 4 processes: their intake, absorption, distribution and excretion. Disturbance in any of these processes in diverse pathophysiologic states may cause electrolyte imbalance.
- Among the important components in electrolyte imbalance, abnormalities in serum levels of sodium (hypo- and hypernatraemia), potassium (hypo- and hyperkalaemia). calcium (hypo- and hypercalcaemia) and magnesium (hypo and hypermagnesaemia) are clinically more important.
- General principles of electrolyte imbalance are as under :

i)Electrolyte imbalance in a given case may result from one or more conditions.

ii) Resultant abnormal serum level of more than one electrolyte may be linked to each other e.g. abnormality in serum levels of sodium and potassium: calcium and phosphate.

iii) Generally, the reflection of biochemical serum electrolyte levels is in the form of metabolic syndrome and clinical features .

BASIC MECHANISM INVOLVED IN THE PROCESS OF INFLAMMATION AND REPAIR:

INFLAMMATION - Self-defence is a property of living organism. Inflammation is a direct tissue response to noxious or injurious external/internal stimuli. Inflammation can occur in response to any thing that damages the tissue, e.g.:

- Toxic chemicals: acid, alkali etc.
- Physical factors: heat, cold, electricity, radiation, trauma - microorganism and their metabolic by-product.
- Immune response: hypersensitivity, immune complex, auto immune reactions. Every organ/tissue type is susceptible to inflammation.

Degree and nature of the inflammatory response depends on person's state of health, nutrition, immunity, nature and severity of noxious stimuli.

CLINICAL SIGNS OF INFLAMMATION -

There are four main signs of inflammation. These are:

1.Ruber : Redness

2.Tumour : Swelling

3.Calor : Heat

4.Dolor: Pain, Loss of function

TYPES OF INFLAMMATION -

Three main types of inflammation are:

(a) Latent Inflammation: When trauma or injury is extremely mild, the response may be immediate and brief. Inflammation subsides before it is noticeable.

(b) acute Inflammation: To certain type of trauma (injury) tissue react sharply by undergoing severe changes, such response is acute inflammation. Tissue changes occurring in acute inflammation may subside partly, completely after overcoming the trauma.

(c) Chronic Inflammation: Inflammation of prolonged duration. Trauma continues to elicit response in subsidised form. The resultant inflammation is called chronic inflammation.

MECHANISM OF INFLAMMATION

- **Haemodynamic Changes -**

- Inflammatory response result from changes in the vascular flow and calibre of small blood vessels in the injured tissue. The sequence of these changes is given as:
  1. Irrespective of the type of cell injury, immediate vascular response is of **transient vasoconstriction** of arterioles. With mild form of injury, the blood flow may be re-established in 3-5 seconds while with more severe injury the vasoconstriction may last for about 5 minutes,

  2. Next follows **persistent progressive vasodilatation** which involves mainly the arterioles but, affects other components of the microcirculation like venules and capillaries(to a lesser extent). This change is obvious within half an hour of injury. Vasodilatation results in increased blood volume in microvascular bed of the area, which is responsible for redness and warmth at the site of acute inflammation.

  3. Progressive vasodilatation, may elevate the **local hydrostatic pressure** resulting in transudation of fluid into the extracellular space. This is responsible for swelling at the local site of acute inflammation.

  4. **Slowing or stasis** of microcirculation causes increased concentration of red cells and hence raised blood viscosity.

  5. Stasis or slowing is followed by **leucocytic margination** or peripheral orientation of leucocytes (mainly neutrophils) along the vascular endothelium. The leucocytes stick to the vascular endothelium and then move and migrate through the gaps between the endothelial cells into the extravascular space.This process is known as **emigration** in inflammation.

- **Altered blood flow(vascular permeability) -**

Pathogenesis :

- Inside and around of the tissue in which inflammation already occured, there is accumulation of oedema fluid in the interstitial compartment which comes from blood plasma by its escape through the endothelial wall of peripheral vascular bed.
- In the initial stage, the escape of fluid is due to vasodilation and elevation in hydrostatic pressure. This is transudate in nature.
  The inflammatory oedema, exudate appears by increased vascular permeability of microcirculation.
- Appearance of inflammatory oedema due to increased vascular permeability of microvascular bed is explained by **Starling's hypothesis.**
  According to this, normally the fluid balance is maintained by two opposing sets of forces which are as follows-
  (i) Forces that cause **outward movement** of fluid from microcirculation: These are intravascular hydrostatic pressure and colloid osmotic pressure of interstitial fluid.
  (ii) Forces that cause **inward movement** of interstitial fluid into circulation: These are intravascular colloid osmotic pressure and hydrostatic pressure of interstitial fluid.
- If any amount of fluid is left in the interstitial compartment ,it is drained away by lymphatics and no oedema occurs.
- But, in inflamed tissues, the endothelial lining of microvasculature becomes more leaky.
- As a result, intravascular colloid osmotic pressure decreases and osmotic pressure of the interstitial fluid increases resulting in excessive outward flow of fluid into the interstitial compartment which is exudative inflammatory oedema.

MEDIATORS OF INFLAMMATION

- These are large number of endogenous chemical substances which mediate the process of acute inflammation.
- Common properties of mediators of inflammation are as under:

1)These mediators are released either from the cells or derived from plasma proteins: Cell-derived mediators are released either from their storage in the cell granules or are synthesised in the cells. Liver is the most common site of synthesis of plasma derived mediators. After their release from the liver, these mediators require activation.

2) All mediators are released in response to certain stimuli. These stimuli may be injurious agents, dead and damaged tissues, or even one mediator stimulating release of another. The latter are called secondary mediators which may perform the function of the initial mediator or may have opposing action.

3) Mediators act on different targets. They may have similar action on different target cells or differ in their action on different target cells. They may act on cells which formed them or on other body cells.

4) Range of actions of different mediators are: increased vascular permeability, vasodilatation, chemotaxis, fever, pain and tissue damage.

5) Mediators have short lifespan after their release. After release, they are rapidly removed from the body by various mechanisms e.g. by enzymatic inactivation, antioxidants, regulatory proteins or may even decay spontaneously.

- Two main groups of substances acting as chemical mediators of inflammation are those released from the cells and those from the plasma proteins.

I Cell derived mediators-

1.Vasoactive amines (Histamine, 5- Hydroxytryptamine, Neuropeptides)

2.Arachadonic acid metabolites

3.Lysosomal components

4.Platelet activating factor (PAF)

5.Cytokines

6.Free radicals: Oxygen metabolites and nitric oxide.

II Plasma Protein -derived Mediators (Plasma Proteases)-

1.The kinin system

2.The clotting system

3.The fibrinolytic system

4. The complement system

HEALING OF SKIN WOUNDS

- Healing of skin wounds provides a combination of regeneration and repair. .Wound healing takes place in two ways:

1.Healing by first intention (primary union)

2. Healing by second intention (secondary union).

HEALING BY FIRST INTENTION (PRIMARY UNION)

This is defined as healing of a wound which has the following characteristics:

i) clean and uninfected;

ii) surgically incised;

iii) without much loss of cells and tissue; and

iv) edges of wound are approximated by surgical sutures. The sequence of events in primary union are

1. **Initial haemorrhage.** Immediately after injury, the space between the approximated surfaces of incised wound is filled with blood which then clots and seals the wound against dehydration and infection.

2. **Acute inflammatory response.** This occurs within 24 hours with appearance of polymorphs from the margins of incision. By 3rd day, polymorphs are replaced by macrophages.

3. **Epithelial changes.** The basal cells of epidermis from both the cut margins start proliferating and migrating towards incisional space in the form of epithelial spurs. A well approximated wound is covered by a layer of epithelium in 48 hours. The migrated epidermal cells separate the underlying viable dermis from the overlying necrotic material and clot, forming scab which is cast off. The basal cells from the margins continue to divide. By 5th day, a multilayered new epidermis is formed which is differentiated into superficial and deeper layers.

4. **Organisation** By 3rd day, fibroblasts also invade the wound area. By 5th day, new collagen fibrils start forming which dominate till healing is completed. In 4 weeks, the scar tissue with scanty cellular and vascular elements, a few inflammatory cells and epithelialised surface is formed.

5. **Suture tracks.** Each suture track is a separate wound and follows same phenomenon as in healing of the primary wound i.e. filling the space with haemorrhage, some inflammatory cell reaction , epithelial cell proliferation along the suture track from both margins, fibroblastic proliferation and formation of young collagen. When sutures are removed around 7^{th} day, much of epithelialised suture track is absorbed.

HEALING BY SECOND INTENTION (SECONDARY UNION)

This is defined as healing of a wound having the following characteristics :

i)Open with a large tissue defect, at times infected;

ii)having extensive loss of cells and tissues; and

iii) the wound is not approximated by surgical sutures but is left open.

The sequence of events in secondary union is as follows:

1.**Initial haemorrhage.** As a result of injury, the wound space is filled with blood and fibrin clot which dries.

2.**Inflammatory phase.** There is an initial acute inflammatory response followed by appearance of macrophages which clear off the debris as in primary union.

3.**Epithelial changes.** As in primary healing, the epidermal cells from both the margins of wound proliferation and migrate into the wound in the form of epithelial spurs till they meet in the middle and re- epithelialise the gap completely.

4. **Granulation tissue.** Main bulk of secondary healing is by granulations. Granulation tissue is formed by proliferation of fibroblasts from the adjoining viable elements.

5.**Wound contraction.** Due to the action of myofibroblasts present in granulation tissue, the wound contracts to one third to one fourth of its original size.

6. **Presence of infection.** Bacterial contamination of an open wound delays the process of healing due to release of bacterial toxins that provoke necrosis suppuration and thrombosis.