GENERAL PATHOLOGY

LECTURE - 3

CELL INJURY

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CELL INJURY

- **No adaptive response or adaptive capacity is exceeded**
- **"Any change that results in a loss of the ability to maintain normal or adapted homeostatic state" -- Cell Injury.**

Severity of Cell Injury

Dependent on

• Severity and type of stress	**Acid – strong, weak**
• Blood Supply and Nutrition	**Single / double**
• Metabolic state of cell	**Active / resting**
• Previous state of cell.	**Adaptive / normal**

Severity of Cell Injury

Dependent on

intensity of injury
duration of injury

Hot Water
1 sec at 160^0
2 min at 122^0
45 min at 109^0

type of cell involved

Hypoxia
Brain Cells 4 minutes
Renal Cells 20 minutes

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Cellular Patterns and Response to Stress

- Reversible Cell Injury
  1. Cell swelling
  2. Fatty Change
- Irreversible Cell Injury
  1. Necrosis
     - Coagulative
     - Liquefactive
     - Fat
     - caseous
  2. Apoptosis

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Cell Injury-Causes

A Generalized Listing

- **Oxygen** (Too much or ischemia, hypoxia)
- **Physical agents** (heat, cold, radiation, trauma, electricity)
- **Chemical agents and drugs** (CN^-, Hg, CO, EtOH, drugs, ROS)
- **Infectious organisms** (viruses, bacteria, fungi)
- **Immunologic reactions** (anaphylaxis, autoimmune diseases)
- **Genetic derangements** (Sickle cell disease, Hypotrichosis)
- **Nutritional imbalances** (vitamins def/x's, malnutrition, x's calories)
- **Aging**

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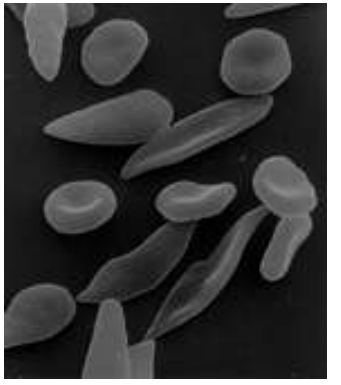
- Sickle cell disease
- The sickling occurs because of a mutation in the hemoglobin gene "HbSS"
- sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ, resulting in ischemia, pain, and often organ damage.



Hypotrichosis – Hairlessness

Infectious, immunological and inflammation

- Pathogens cause damage when they invade cells (entry and exit damage)
- Pathogens produce toxins (endotoxins -- gram negative bacteria)
- Hypersensitivity reactions can cause tissue damage
- Phagocytic cells cause peripheral damage
- Complement and proteases can cause damage
- Antibodies can cause membrane damage and destroy cell junctions

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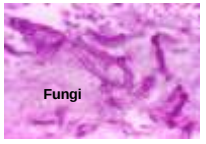
- Infectious agents
  - Viruses.
  - *Chlamydia.*
  - *Rickettsia.*
  - Bacteria.
    - Gram positive.
    - Gram negative.
    - Mycobacteria.
    - Spirochetes.
  - Fungi.
  - Parasites.
    - Protozoans.
    - Worms.



Cysts containing *Toxoplasma gondii* in brain

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- Immunologic reactions
  - *Anaphylaxis.*
    - Exposure to foreign protein resulting in urticaria, pruritus and angioedema with life-threatening vascular collapse (shock).
  - *Loss of tolerance* by T cells that should not attack the "self."
    - May lead to *autoimmune disease* if a foreign antigen (*e.g.,* viral protein) looks like (mimics) a self-antigen to the immune system and the self-antigen is no longer "tolerated" but is attacked.
- Genetic defects
  - Single amino acid substitution (hemoglobin S in sickle cells).
  - Enzyme deficiencies.
  - Anatomic malformations (but many are sporadic).

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- Oxygen deprivation
  - *Hypoxia*, or decreased O_2 in the blood, interrupts aerobic respiration in cells.
  - *Ischemia* is a decrease or loss of blood supply, a consequence of which is hypoxia, and also loss of nutrients such as glucose.
  - Causes range from choking, to pneumonia with ↓ pulmonary function, to carbon monoxide (CO) poisoning wherein CO binds so avidly to hemoglobin that O_2 has no binding site.
- Chemical agents
  - Everything in moderation: ↑↑↑ Blood glucose → shift of H_2O into blood → hyperosmotic coma.
  - Oxygen toxicity with very high partial pressures.
  - Poisons: Alter membrane permeability or enzyme function.
  - Organic and inorganic environmental agents.
  - Therapeutic drugs.

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- Nutritional imbalances
  - Protein-calorie.
  - Vitamins.
  - Excess.
    - Type 2 diabetes mellitus.
    - Atherosclerosis.
- Physical agents
  - Trauma.
  - Temperature.
  - Radiation.
  - Electric shock.
  - Atmospheric pressure.

Aging
- Cellular senescence.
- Degeneration.
- Poor healing.

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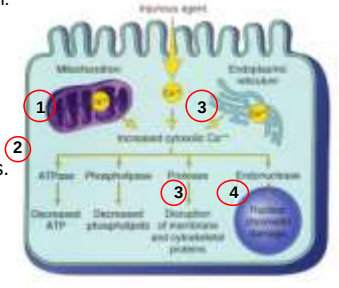
CELL INJURY

- Vulnerable intracellular systems
  1. ATP generation.
     - Mitochondrial aerobic respiration.
  2. Cell membrane integrity.
     - Ionic homeostasis.
     - Osmotic homeostasis.
  3. Protein synthesis.
     - Cell structure and function.
  4. Integrity of the genetic apparatus.
     - Access to DNA.
     - Interactions with DNA.
     - DNA replication.
     - DNA repair mechanisms.



- **Injury at one focus often has a cascade effect**
- **Morphologic reactions occur only after critical biochemical (molecular) damage**

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Cell Injury
Common Biochemical Mechanisms

- **ATP depletion**
- **Loss of calcium homeostasis**
- **Loss of selective membrane permeability**
- **Mitochondrial damage**
- **Oxygen free radical**

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Cell Injury
PATHWAYS OF INJURY

- Interference with Energy Production
- Direct Damage to membranes

GENERAL PATHOLOGY

LECTURE – 4

CELL INJURY Contd.

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1. INTERFERENCE WITH ENERGY PRODUCTION

Hypoxic Injury

- hypoxia = decreased O_2 at the cell
- anoxia = complete lack of O_2
- Hypoxemia = decreased O_2 in the blood
- Ischemia = reduced blood supply to the tissue causes hypoxia

Ischaemia

- Occlusion of the blood vessels
- Failure of the heart to pump enough blood

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Hypoxaemia:

- Too little oxygen in the blood
  - Too little oxygen in the air
  - Failure to properly ventilate the lungs
  - Failure of the lungs to properly oxygenate the blood
  - Failure of the heart to pump enough blood through the lungs
  - Tremendously increased dead space (i.e., pulmonary thromboembolus)

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Haemoglobin problems ("anaemic hypoxia")

- Inadequate circulating red cell mass ("anaemia")
- Inability of haemoglobin to carry the oxygen (carbon monoxide poisoning, methaemoglobinemia)
- High affinity haemoglobins that will not give up their oxygen to the tissues

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Failure of the cytochromes ("histotoxic hypoxia")

- Cyanide poisoning
- Rotenone poisoning
- Dinitrophenol poisoning

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Hypoxic Injury

- Deprives cell of oxygen
- Interrupts oxidative metabolism
- Process of cell injury
  - Na/K pump failure

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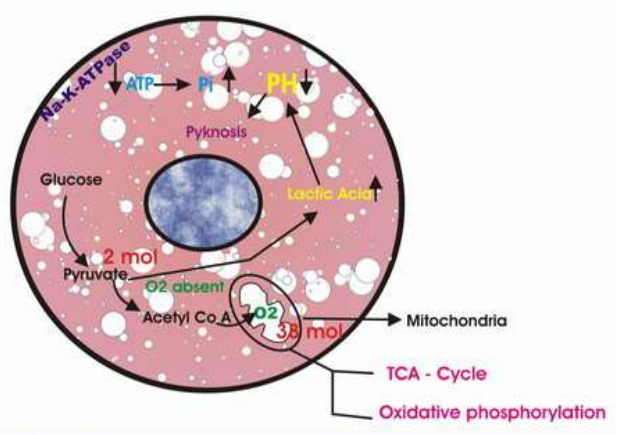

Fig showing that normally in presence of oxygen, 38 mol of ATP is produced from one molecule of glucose breakdown, while in the absence of oxygen only 2 mol of ATP, and that pyruvate get converted into lactic acid resulting in to decrease in pH which causes pyknosis of nucleus. In this process decrease in ATP result in blockage of many functions including Na-K-ATPase.

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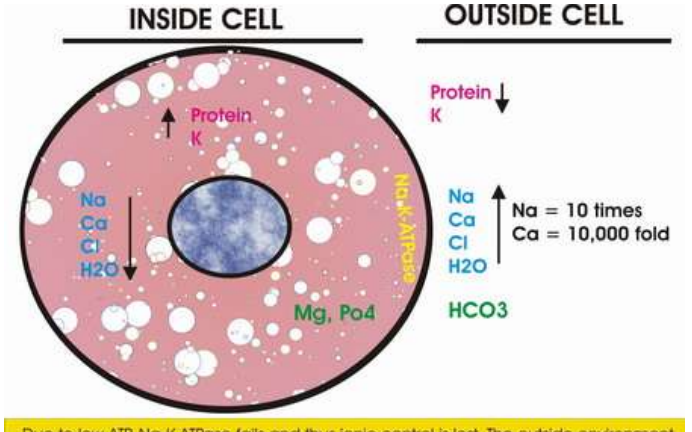

Due to low ATP, Na-K-ATPase fails and thus ionic control is lost. The outside environment is rich in ion and thus those enter the cell as the membrane is a semipermeable membrane. Cell thus starts swelling as water also enters in to the cell. The water level outside cell is very crucial, as the more water outside the cell more it will enter in to the cell.

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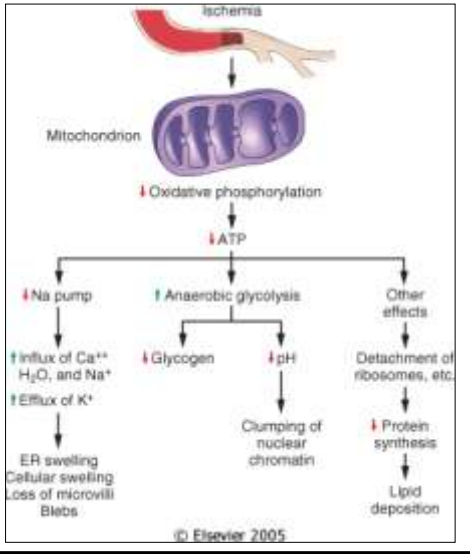

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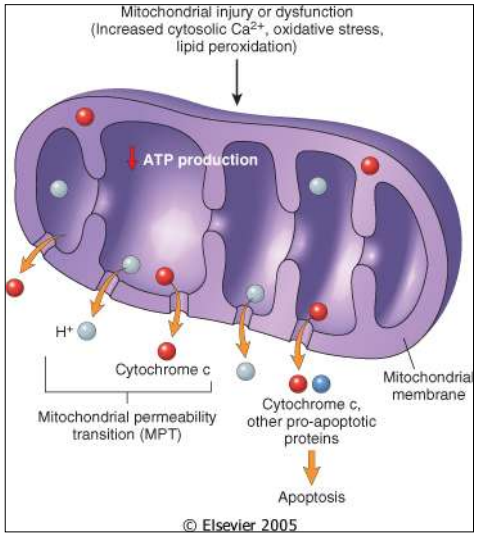
Mitochondrial injury or dysfunction
(Increased cytosolic Ca2+, oxidative stress, lipid peroxidation)
ATP production
H+
Cytochrome c
Mitochondrial permeability transition (MPT)
Cytochrome c, other pro-apoptotic proteins
Mitochondrial membrane
Apoptosis
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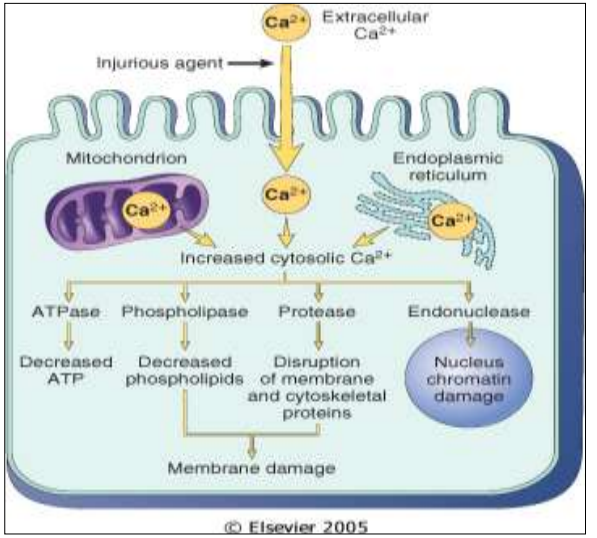
Ca2+ Extracellular Ca2+
Injurious agent
Mitochondrion
Endoplasmic reticulum
Ca2+
Increased cytosolic Ca2+
ATPase
Phospholipase
Protease
Endonuclease
Decreased ATP
Decreased phospholipids
Disruption of membrane and cytoskeletal proteins
Nucleus chromatin damage
Membrane damage
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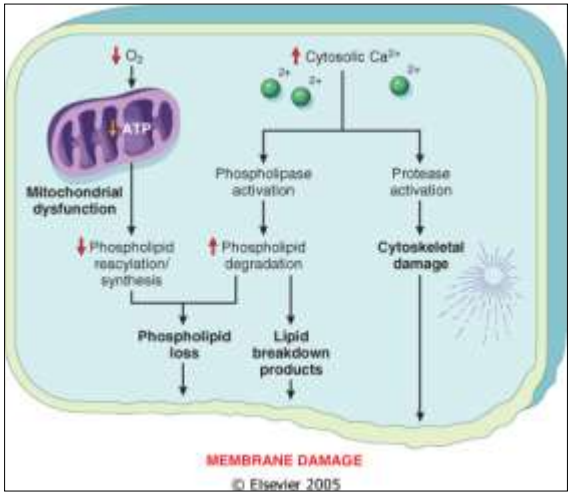
O2
Cytosolic Ca2+
ATP
Mitochondrial dysfunction
Phospholipase activation
Protease activation
Phospholipid resynthesis/ synthesis
Phospholipid degradation
Cytoskeletal damage
Phospholipid loss
Lipid breakdown products
MEMBRANE DAMAGE
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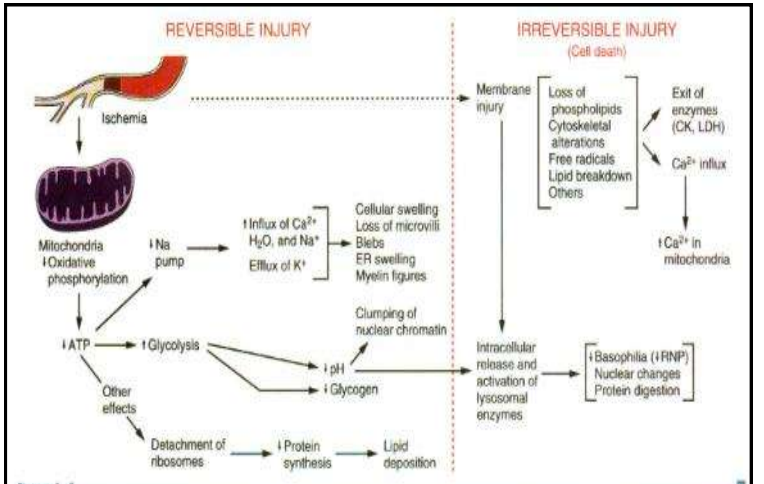
REVERSIBLE INJURY
IRREVERSIBLE INJURY
(Cell death)
Ischemia
Membrane injury
Loss of phospholipids
Cytoskeletal alterations
Free radicals
Lipid breakdown
Others
Exit of enzymes (CK, LDH)
Ca2+ influx
Ca2+ in mitochondria
Mitochondria
Oxidative phosphorylation
Na pump
Influx of Ca2+ H2O, and Na+
Efflux of K+
Cellular swelling
Loss of microvilli
Blebs
ER swelling
Myelin figures
Clumping of nuclear chromatin
ATP
Glycolysis
pH
Glycogen
Other effects
Intracellular release and activation of lysosomal enzymes
Basophilia (RNP)
Nuclear changes
Protein digestion
Detachment of ribosomes
Protein synthesis
Lipid deposition
Figure 1-5
Postulated sequence of events in ischemic injury. Note that although reduced oxidative phosphorylation and ATP levels have a central role, ischemia can cause direct membrane damage. ER, endoplasmic reticulum; CK, creatine kinase; LDH, lactate dehydrogenase; RNP, ribonucleoprotein.

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Ischemia/Hypoxia
Irreversible Cell Injury

Biochemical “point of no return”:

- Inability to restore mitochondial function
  - phospholipase activation ➲mitochondrial permeability transition
- Plasma membrane defects-contributing factors
  - phospholipase activation ➲ degradation of membrane phospholipids
  - lipid degradation products ➲ membrane detergent effect
  - Ca^{2+} proteases ➲ cytoskeletal degradation➲ membrane detachment

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Ischemia-reperfusion Injury

ATP ↓ ADP ↓ AMP ↓ Adenosine ↓ Inosine ↓ **↑Hypoxanthine**

Ischemia

XDH → **No Rx (no O_2)**

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Ischemia-reperfusion Injury

ATP ↓ ADP ↓ AMP ↓ Adenosine ↓ Inosine ↓ **↑Hypoxanthine Reperfusion**

Reperfusion

XDH ↓ Ca-activated **protease** → XO

XO → Uric Acid + ***Superoxide***

O_2 → PMNs

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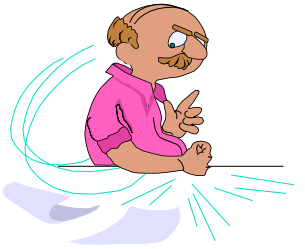
3 R’s of success:



Respect for self,
Respect for others and
Responsibility for all your actions

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