Chemical and Biochemical Mechanism Of Cell Injury.

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Cell Injury

When the cell is exposed to an injurious agent or stress, a sequence of events follows that is loosely termed **cell injury**.

- Cell injury is **reversible** up to a certain point
- If the stimulus persists or is severe enough from the beginning, the cell reaches a point of no return and suffers **irreversible** cell injury and ultimately **cell death**.
- **Cell death**, is the ultimate result of cell injury

Causes of Cell Injury

1) Oxygen Deprivation (*Hypoxia).* It is a common cause of cell injury and cell death.

-***Hypoxia*** can be due to :

A- inadequate oxygenation of the blood due to Cardio respiratory failure.

B- loss of the oxygen-carrying capacity of the blood, as in anemia or carbon monoxide poisoning.

- Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die.

2) Physical Agents :

- Mechanical trauma,
- Burns,
- Deep cold,
- Sudden changes in atmospheric pressure,
- radiation, and electric shock,

3) Chemical Agents and Drugs

- oxygen, in high concentrations
- *poisons*, such as arsenic, cyanide, or mercuric salts
- environmental and air pollutants
- insecticides, herbicides, industrial and occupational hazards
- alcohol and narcotic drugs and therapeutic drugs

4) Infectious Agents e.g. bacteria, fungi, viruses and parasites, etc.

5) Immunologic Reactions.

6) Genetic Derangements.

7) **Nutritional Imbalances**

4 weak points of the cell

- Cell membrane integrity, critical to cellular ionic and osmotic homeostasis
- ATP synthesis, largely via mitochondrial aerobic respiration
- Protein synthesis (RER)
- Integrity of the genetic apparatus (nucleus)

- The structural and biochemical components of a cell are so integrally connected that regardless of the initial locus of injury, multiple secondary effects rapidly occur (Ripple effect).

Mechanisms of Cell Injury:

Two models:

a. Ischemic injury

b. Chemical injury

Ischemia vs Hypoxia

- Loss of blood supply
- ↓ed O2 as well as ↓ed delivery of other nutrients
- ↓ed removal of toxic waste products of the cells so there is accumulation of toxic substances, e.g Lactic acid.
- Quicker and More severe injury than with just lack of Oxygen

- Lack of Oxygen in tissues
- Maybe due to ischemia or due to other causes like due to less RBCs in the blood, or less Oxygen in the atmosphere etc.
- Less severe injury than with Ischemia

MECHANISM OF CELL INJURY

1. Depletion of ATP
2. Mitochondrial Damage
3. Influx of intracellular calcium & loss of calcium homeostasis
4. Accumulation of oxygen-derived free radicals (oxidative stress)
5. Defects In Membrane Permeability

1. DEPLETION OF ATP

- ATP is required for many synthetic and degradative processes within the cell
- ATP depletion and decreased ATP synthesis are associated with both hypoxic and chemical (toxic) injury

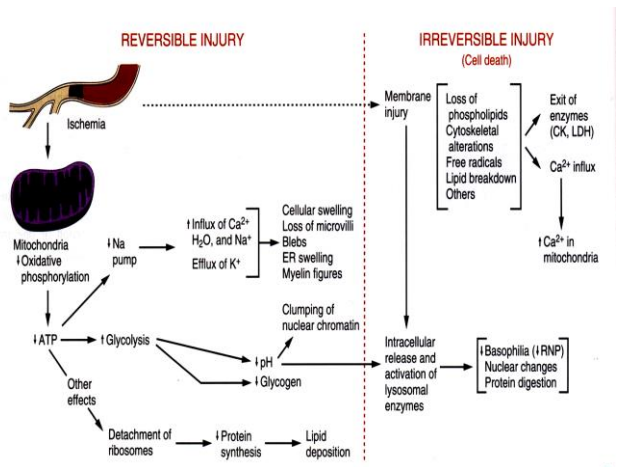
ATP is produced in two ways.

- The major pathway is oxidative phosphorylation of ADP
- The second is the glycolytic pathway, which generate ATP in absence of oxygen using glucose derived from glycogen

Effects of depleted ATP

- The activity of the plasma membrane energy-dependent sodium pump is reduced. It causes sodium to accumulate intracellular and potassium to diffuse out of the cell causing cell swelling, and dilation of the endoplasmic reticulum.
- In ischemia(reduce o2 supply), oxidative phosphorylation ceases and cells rely on glycolysis for energy production (anaerobic metabolism) resulting in depletion of *glycogen stores*. Glycolysis results in the accumulation of lactic acid which reduces the intracellular pH, resulting in decreased activity of many cellular enzymes.

- Failure of the Ca2+ pump leads to influx of Ca2+, with damaging effects on numerous cellular components.
- Ribosome's detach from the RER and polysomes breakdown into monosomes, leading to reduction in protein synthesis.
- Ultimately, irreversible damage to mitochondrial and lysosomal membranes occurs, and cell undergoes necrosis.
- In cells deprived of oxygen or glucose, proteins may become misfolded, and trigger the unfolded protein response leading to cell injury and even death



2. Mitochondrial Damage

- Mitochondria are important targets for all types of injury, including hypoxia and toxins

Mitochondria can be damaged by

A- Increases of cytosolic Ca2+

B- Oxidative stress

C- Breakdown of phospholipids, and by

D- Lipid breakdown products

- Mitochondrial damage results, mitochondrial permeability transition, present in the inner mitochondrial membrane.
- In the initial phase it is reversible but once mitochondrial permeability transition is irreversible it becomes a deathblow to the cell
- Mitochondrial damage can also be associated with leakage of cytochrome *c* into the cytosol

Seen just before cell death

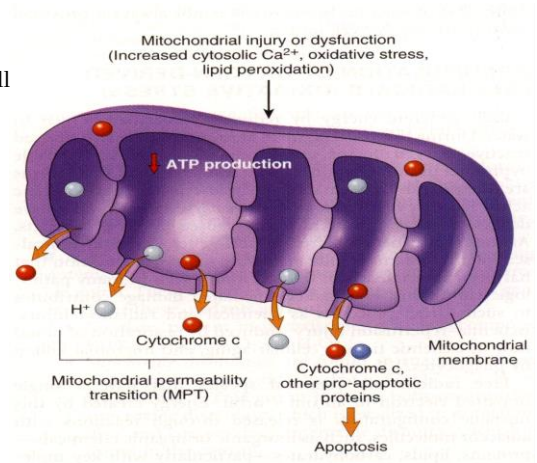


FIGURE 1–12 Mitochondrial dysfunction in cell injury.

3.Influx of intracellular calcium & loss of calcium homeostasis.

Ischemia causes an increase in cytosolic calcium concentration.

Increased Ca2+ in turn activates a number of enzymes**, e.g**.

- *ATPases* (ATP depletion),

-*Phospholipases* (which cause membrane damage),

- *Proteases* (which break down both membrane and cytoskeleton proteins), and

-*Endonucleases* (which are responsible for DNA and chromatin fragmentation).

Effects of excess calcium in the cytosol

Cut-off point between reversible cell injury and cell death??

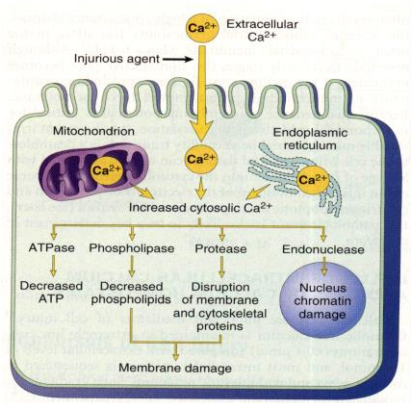


FIGURE 1–13 Sources and consequences of increased cytosolic calcium in cell injury. ATP, adenosine triphosphate.

4. Accumulation of oxygen-derived free radicals (oxidative stress)

Free radicals are chemical species that have single unpaired electron in an outer orbit.

➢ They are initiated within cells in several ways:

a) Absorption of radiant energy (e.g., ultraviolet light, x-rays).

b) Enzymatic metabolism of exogenous chemicals or drugs .

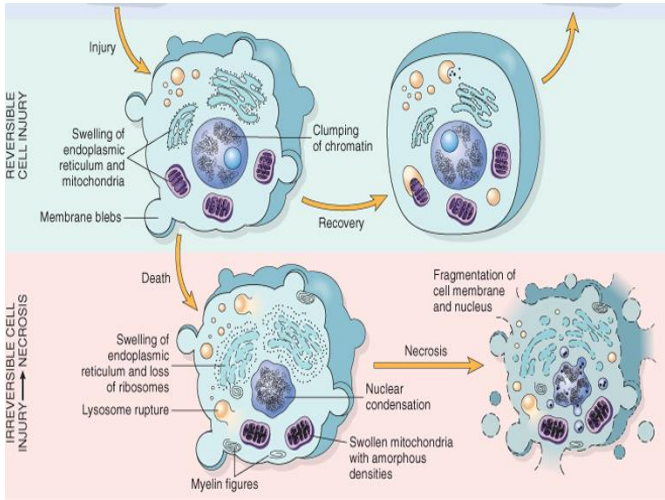
c) The reduction-oxidation reactions that occur during normal metabolic processes normal produce small amounts of toxic intermediates, these include superoxide anion radical (O2-), hydrogen peroxide (H2O2), and hydroxyl ions (OH).

d) Transition metals such as iron and copper.

e) **Nitric Oxide** (NO), an important chemical mediator generated by various cells, can act as a free radical.

➢ Effects of these reactive species are

- Lipid peroxidation of membranes: result in extensive membrane, organelle, and cellular damage.
- Oxidative modification of proteins. resulting in protein fragmentation.
- Lesions in DNA. This DNA damage has been implicated in cell aging and malignant transformation of cells.



Mechanism of chemical injury:

Most chemicals do not produce cell injury directly by themselves, but once they are metabolized in the body, the metabolites are the injurious agent:

Example is Carbon tetrachloride poisoning