HM/CH-1/L-4

CELL INJURY

Attempts at restoration of blood supply

- Cell injury due to oxygen deprivation: depends upon duration of ischaemia and blood restoration
- Cell injury accentuated by restoration of perfusion (ischaemia-reperfusion injury) and subsequent events (liberation of toxic free radicals)

3 different consequences:

- Ishaemia to reversible cell injury
- Ischaemia to reperfusion injury
- Ischaemia to irreversible injury

Ischaemia-reperfusion injury and free-radical mediated cell injury

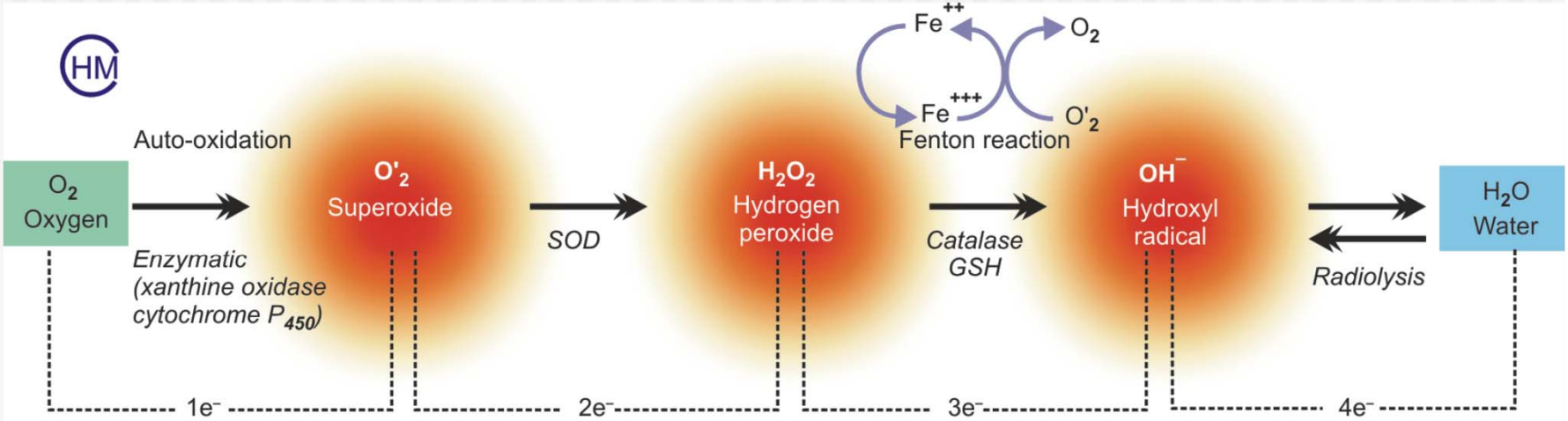
Underlying mechanism: 3 components

1. Calcium overload
2. Generation of reactive oxygen radicals
3. Subsequent inflammatory reaction

Ischaemia-reperfusion injury and free-radical mediated cell injury

Generation of oxygen free radicals:

- Superoxide oxygen (O_2): 1 electron transfer
- Hydrogen peroxide (H_2O_2): 2 electrons transfer
- Hydroxyl radicals (OH^-): 3 electrons transfer



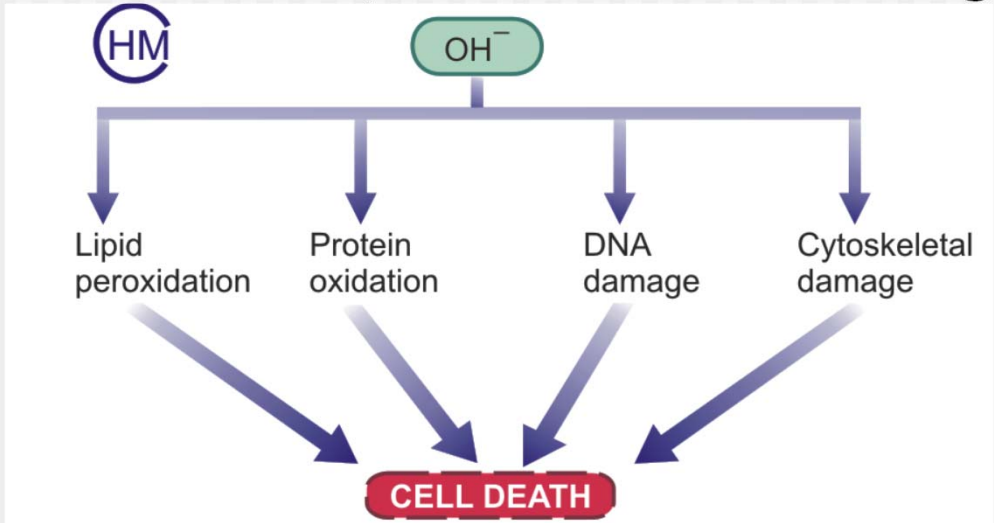
Web Image 3.8: Mechanisms of generation of free radicals by four electron step reduction of oxygen. (SOD = superoxide dismutase; GSH = glutathione peroxidase).

Other oxygen free radicals

- Superoxide free radicals from Fenton reaction
- Nitric oxide (NO) to ONOO
- Halides: Cl to HOCl
- Exogenous sources e.g. tobacco, pollutants

Cytotoxicity of oxygen free radicals

- In physiologic and pathologic processes
- Unstable, destroyed
- Net effect:rate of generation *vs* destruction
- If not degraded cause oxidative stress
- Most reactive OH^-; membrane damage



Web Image 3.9: Mechanism of cell death by hydroxyl radical, the most reactive oxygen species.

Conditions with free radical injury

- Ischaemia reperfusion injury
- Ionising radiation
- Chemical toxicity
- Chemical carcinogenesis
- Hyperoxia
- Cellular ageing
- Microbial injury
- Inflammatory damage
- Destruction of tumour cells
- Atheroscelrosis

Antioxidants

- Vitamin E, A, C
- Sulfhydryl-containing compounds (cysteine, gltathione)
- Serum proteins e.g. ceruloplasmin, transferrin

PATHOGENSIS OF CHEMICAL INJURY

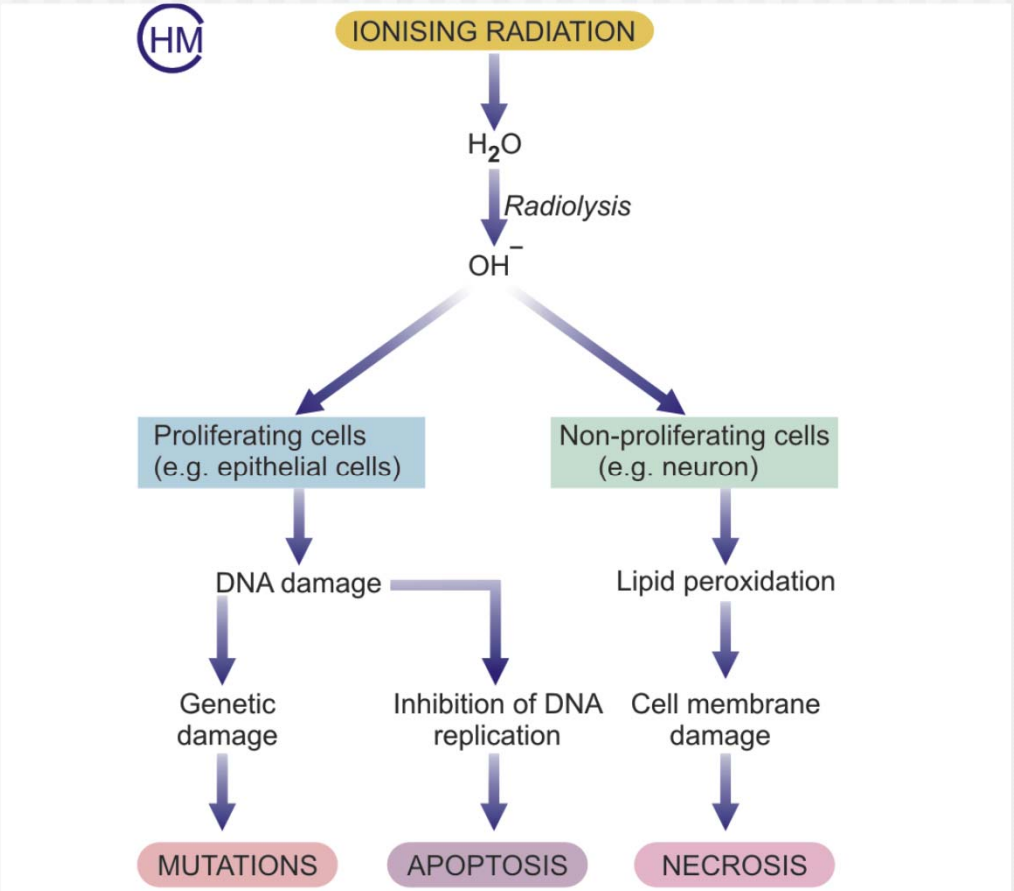
- Direct cytotoxic effects:

  e.g. chemotherapeutic agents in cancer, toxic heavy metals (cyanide, mercury, lead, iron)
- Conversion to reactive toxic metabolites:

  e.g. CCl_4, acetaminophen, bromobenzene

PATHOGENSIS OF PHYSICAL INJURY

- Mechanical injury
- Thermal trauma
- Electricity
- Rapid changes in atmospheric pressure
- Radiation injury (UV, ionisation)



Web Image 3.10: Mechanisms of cell injury by ionising radiation.