Pathophysiology introduction

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- Pathology is literally the study (logos) of suffering (pathos).

- Pathology: scientific study of changes in the structure and function of the body in disease.

- Pathology

- General: concerned with basic reactions of cell and tissue to abnormal stimuli
- Systemic: concerned with specific organs and tissues to more or less well-defined stimuli

Pathophysiology: study of disordered function (physiological changes) and breakdown of homeostasis in diseases (biochemical changes)

Four aspects of a disease process that form the core of pathology

- Etiology
- Pathogenesis
- Morphological changes
- Clinical significance

1. Etiology
   - Genetic
   - Acquired
2. Pathogenesis: sequence of events in response of cell/tissue to etiological agent
3. Morphologic changes: structural alterations in cells or tissues characterstic of disease.
4. Clinical manifestations: morphologic changes influence normal function and determine the clinical features (symptoms and signs)

Basic principles of cell injury and adaptation

Homeostasis

Homeostasis

- Homeostasis (ho¯ me¯–o¯–STA¯ –sis; homeo– sameness; –stasis standing still) is the condition of equilibrium (balance) in the body's internal environment due to the constant interaction of the body's many regulatory processes

- Homeostasis is a dynamic condition.

- In response to changing conditions, the body's equilibrium can shift among points in a narrow range that is compatible with maintaining life

- An important aspect of homeostasis is maintaining the volume and composition of body fluids.

Control of Homeostasis

- Disruptions in homeostasis come from the external environment in the form of physical insults, from internal environment and from psychological stresses.

- Most cases the disruption of homeostasis is mild and temporary, and the responses of body cells quickly restore balance in the internal environment

- Some cases the disruption of homeostasis may be intense and prolonged
- The body has many regulating systems that can usually bring the internal environment back into balance
- Mainly the nervous system and the endocrine system

Feedback Systems

A feedback system or feedback loop is a cycle of events in which the status of a body condition is

- Monitored,
- Evaluated,
- Changed,
- Remonitored,
- Reevaluated, and so on.

- Each monitored variable, such as body temperature, blood pressure, or blood glucose level, is termed a controlled condition.

- Any disruption that changes a controlled condition is called a stimulus

Feedback system includes three basic components—

- Receptor,
- Control center, and
- Effector

- Receptor: is a body structure that monitors changes in a controlled condition and sends input to a control center

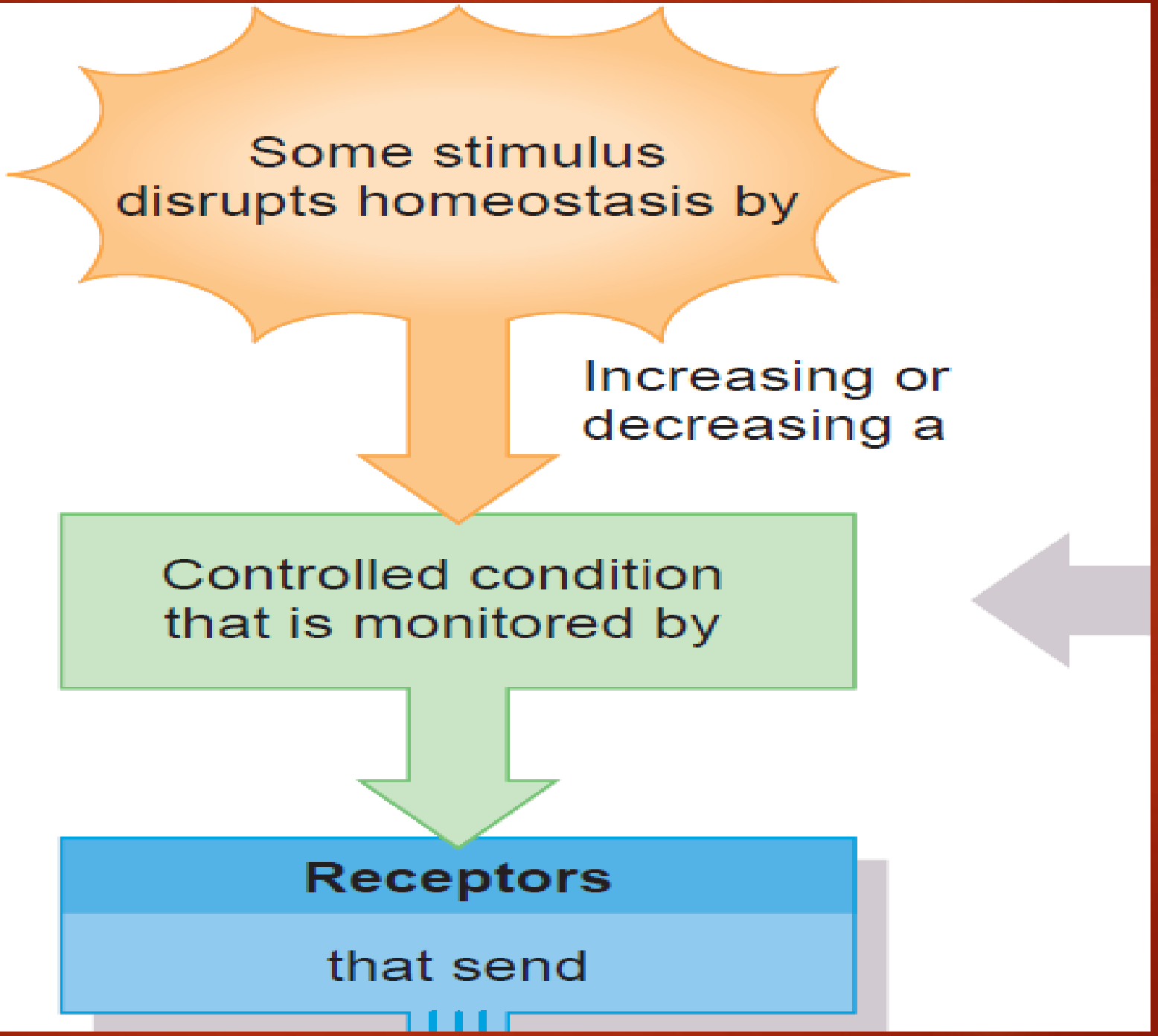
- Input is in the form of nerve impulses or chemical signals

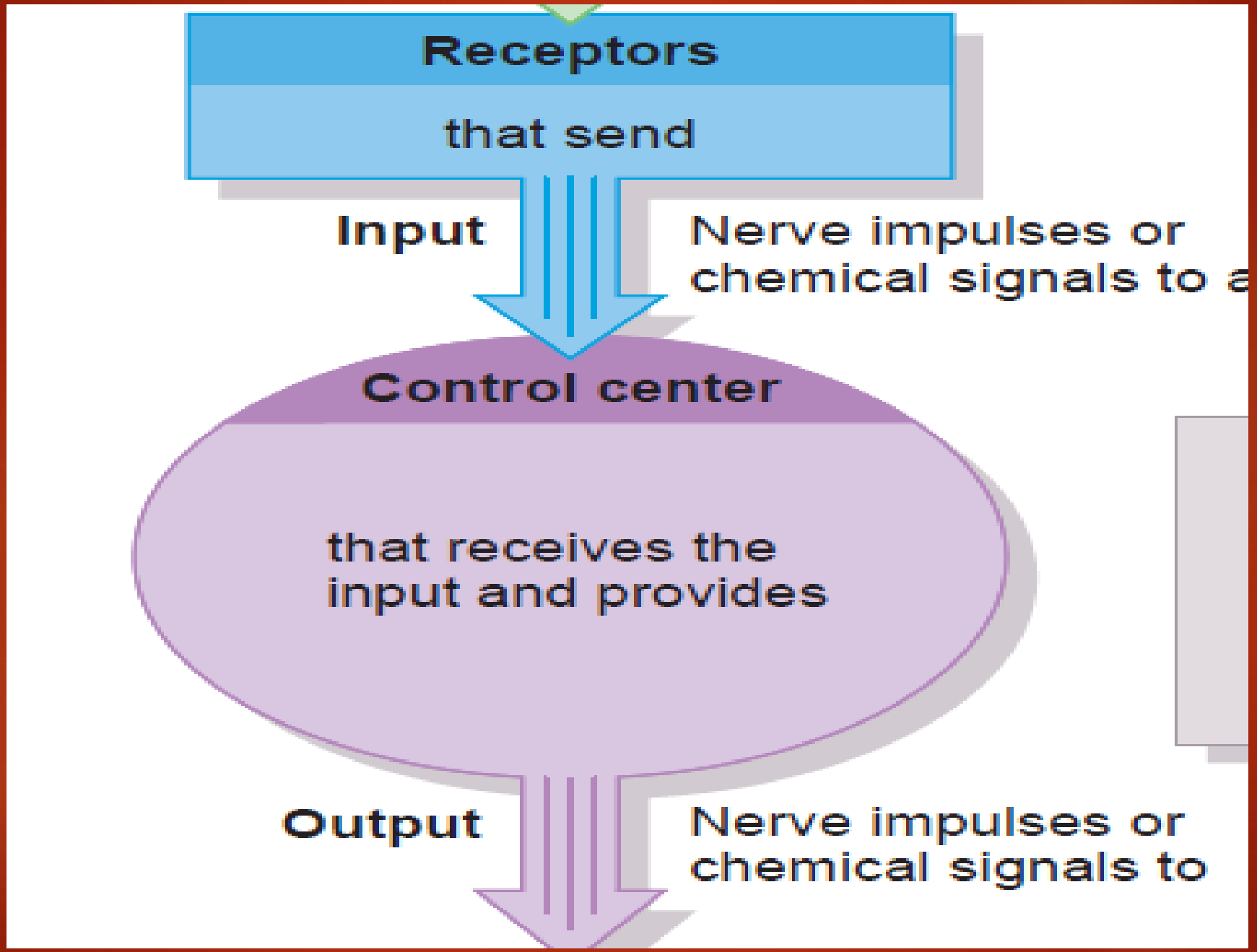
- Control center (in body): sets the range of values within which a controlled condition should be maintained, evaluates the input it receives from receptors, and generates output commands when they are needed

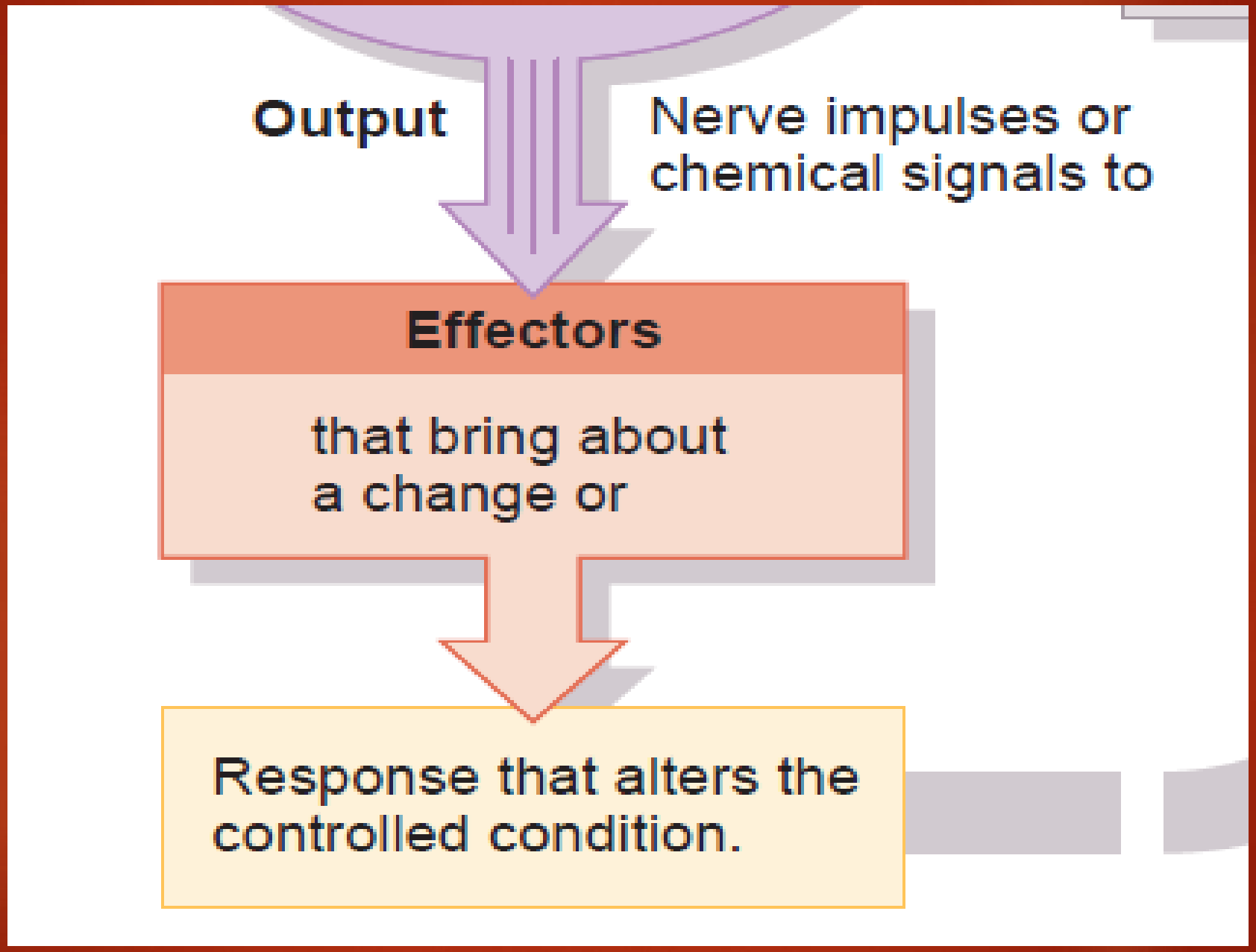
- Output from the control center typically occurs as nerve impulses, or hormones or other chemical signals

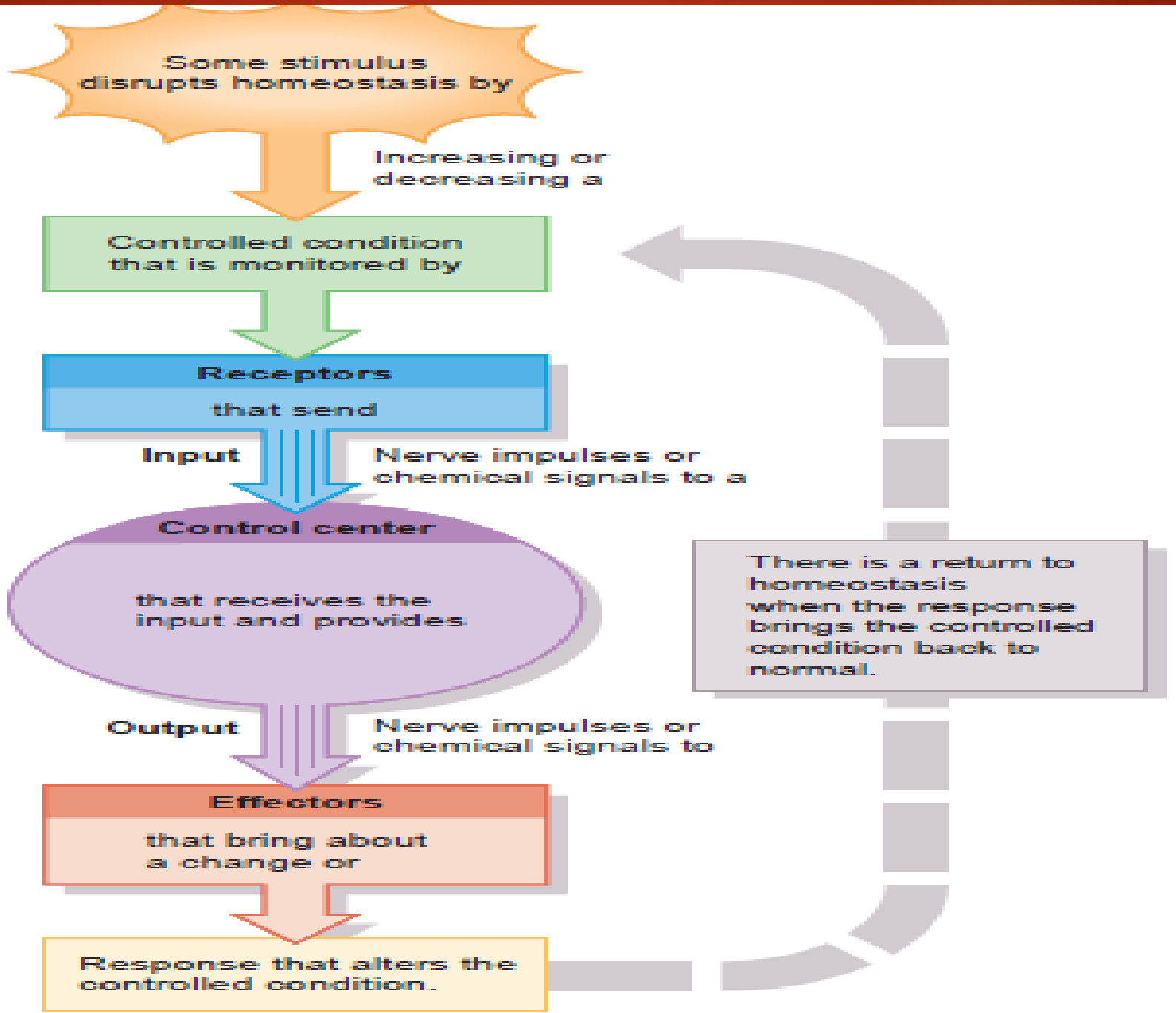
- Effector: is a body structure that receives output from the control center and produces a response or effect that changes the controlled condition.

- Nearly every organ or tissue in the body can behave as an effector


Some stimulus
disrupts homeostasis by
Increasing or
decreasing a
Controlled condition
that is monitored by
Receptors
that send


Receptors
that send
Input
Nerve impulses or
chemical signals to a
Control center
that receives the
input and provides
Output
Nerve impulses or
chemical signals to


Output
Nerve impulses or chemical signals to
Effectors
that bring about a change or
Response that alters the controlled condition.


Some stimulus disrupts homeostasis by
Increasing or decreasing a
Controlled condition that is monitored by
Receptors
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Nerve impulses or chemical signals to a
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Effectors
that bring about a change or
Response that alters the controlled condition.
There is a return to homeostasis when the response brings the controlled condition back to normal.

- A group of receptors and effectors communicating with their control center forms a feedback system that can regulate a controlled condition in the body's internal environment.

- In a feedback system, the response of the system "feeds back" information to change the controlled condition in some way, either negating it (negative feedback) or enhancing it (positive feedback).

Types of feed back system

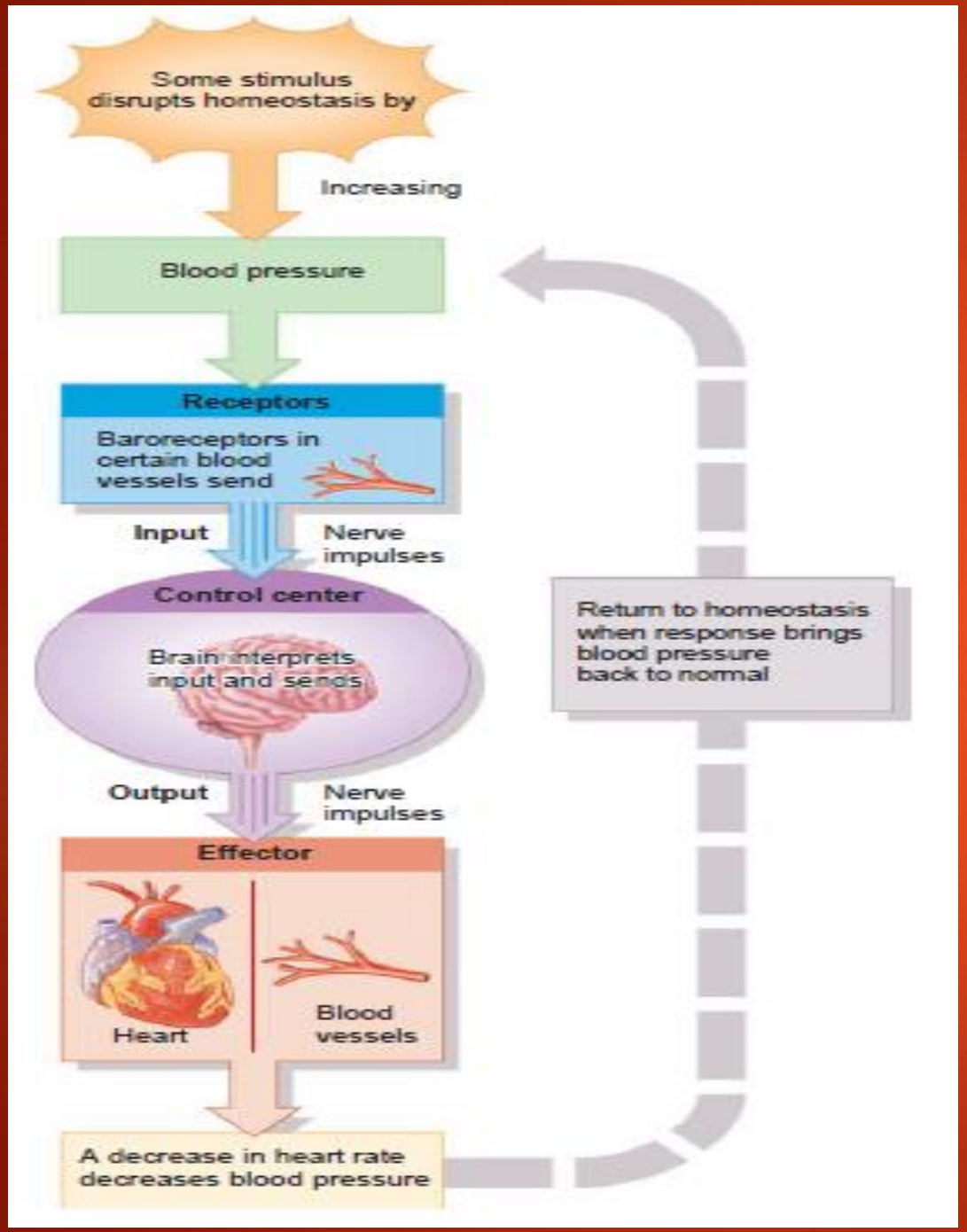
NEGATIVE FEEDBACK SYSTEMS:

- A negative feedback system reverses a change in a controlled condition.

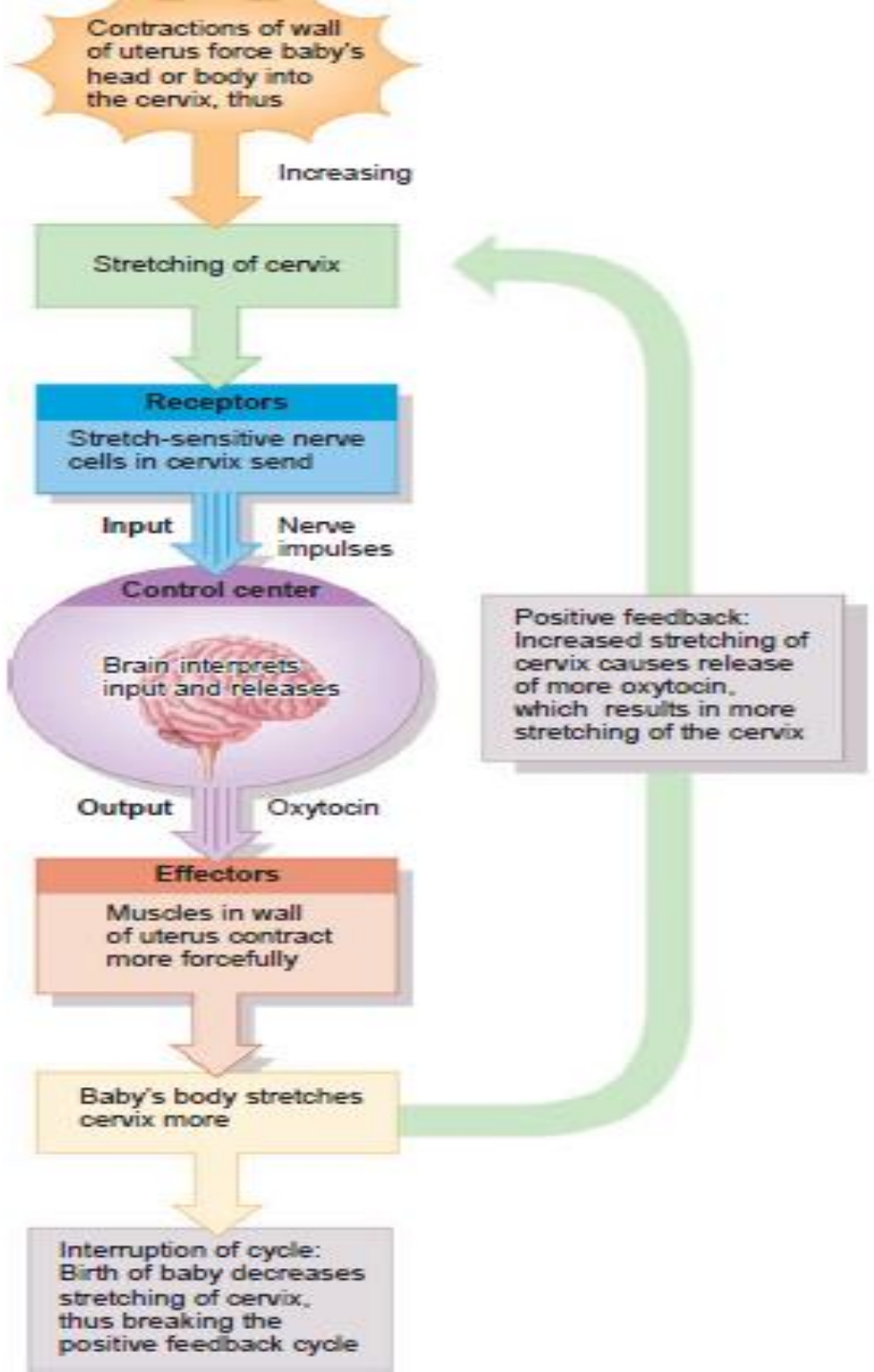
POSITIVE FEEDBACK SYSTEMS:

- The feedback is used to increase the size of the input. By nature, such systems are unstable, and they are most often associated with pathological conditions.
-
- A positive feedback system tends to strengthen or reinforce a change in one of the body's controlled conditions.

- A positive feedback system operates similarly to a negative feedback system, except for the way the response affects the controlled condition
- The control center still provides commands to an effector, but this time the effector produces a physiological response that adds to or reinforces the initial change in the controlled condition.
- The action of a positive feedback system continues until it is interrupted by some mechanism



Homeostatic regulation of blood pressure by a negative feedback system.



Positive feedback control of labor contractions during birth of a baby.

Difference between positive and negative feedback systems

POSITIVE	NEGATIVE
a positive feedback system continually reinforces a change in a controlled condition, some event outside the system must shut it off.	The action of a negative feedback system, by contrast, slows and then stops as the controlled condition returns to its normal state.
If the action of a positive feedback system is not stopped, it can "run away" and may even produce life-threatening conditions in the body.	
Positive feedback systems reinforce conditions that do not happen very often.	Negative feedback systems regulate conditions in the body that remain fairly stable over long periods

Cell responses to stress

- Severe physiologic stresses and some pathologic stimuli may bring about a number of physiologic and morphologic cellular adaptations

- A new but altered steady states are achieved, preserving the viability of the cell and modulating its function as it responds to such stimuli

- In certain pathologic conditions, when cells are damaged beyond repair, and especially if the damage affects the cell's nuclear DNA

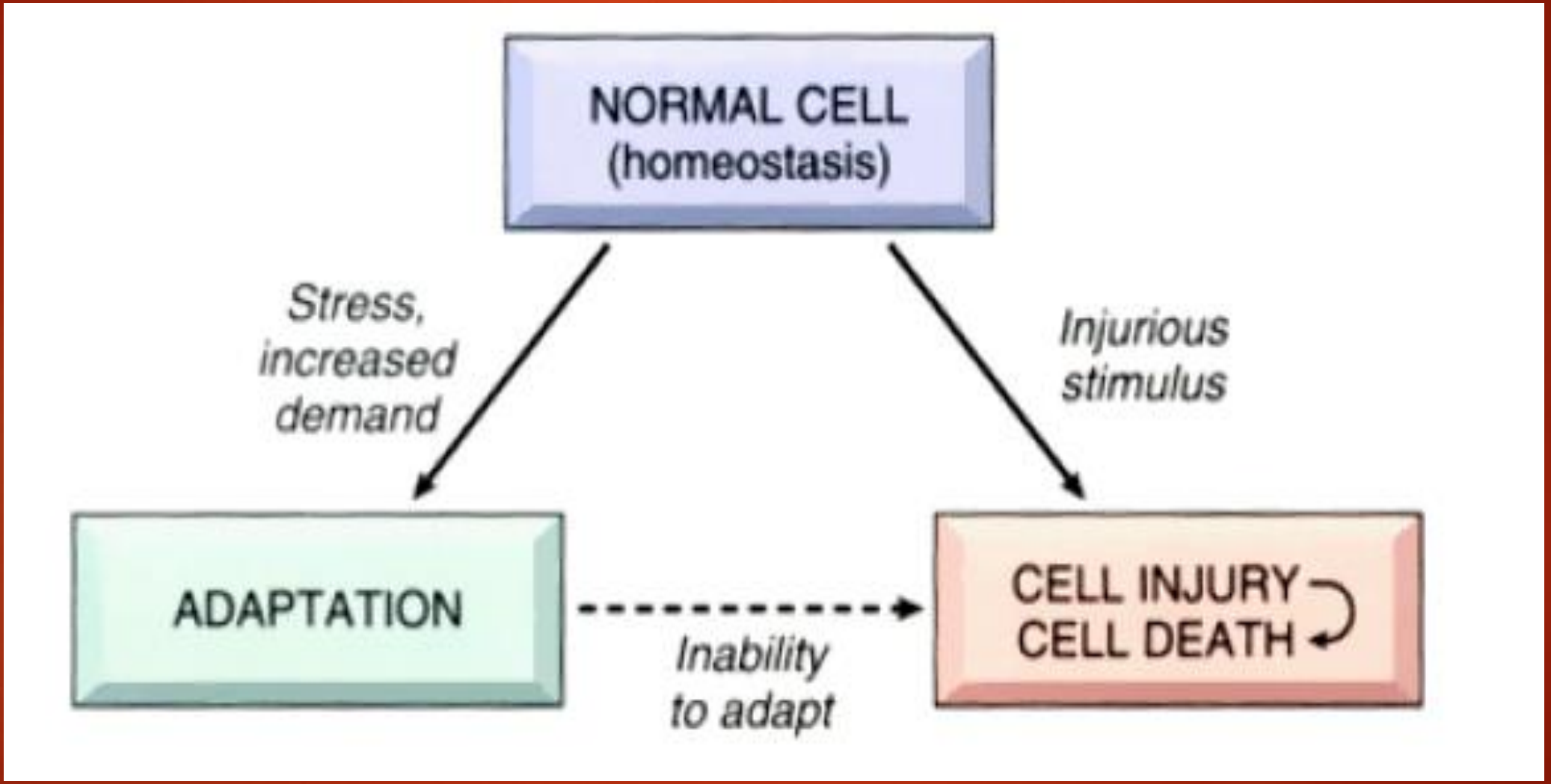
Cell responses to stress

- Exposed to sublethal or chronic stimuli may not be damaged but may show a variety of subcellular alterations.

- Metabolic derangements in cells may be associated with intracellular accumulations

Nature and Severity of Injurious Stimulus	Cellular Response
Altered physiologic stimuli:	Cellular adaptations:
• Increased demand, increased trophic stimulation (e.g. growth factors, hormones)	• Hyperplasia, hypertrophy
• Decreased nutrients, stimulation	• Atrophy
• Chronic irritation (chemical or physical)	• Metaplasia
Reduced oxygen supply; chemical injury; microbial infection	Cell injury:
• Acute and self-limited	• Acute reversible injury
• Progessive and severe (including DNA damage)	• Irreversible injury → cell death
	•••••Necrosis
	•••••Apoptosis
• Mild chronic injury	• Subcellular alterations in various organelles
Metabolic alterations, genetic or acquired	Intracellular accumulations; calcifications
Prolonged life span with cumulative sublethal injury	Cellular aging

Cell responses to stress



a) Adaptation
b) Cell injury
c) Subcellular alterations
d) Intracellular accumulations
e) Calcification
f) Cell aging

Adaptations induced by

1. Factors produced by the responding cells themselves

2. Factors produced by other cells in the environment

3. Activation of various cell surface receptors and downstream signaling pathways

Adaptations associated with

1. Induction of new protein synthesis by the target cells
2. The induction of cellular proliferation
3. Shifting cells from producing one type of proteins to another
4. Markedly overproducing one protein

Types of adaptations

- Hyperplasia: increase in number of cells in an organ or tissue (increase volume of organ)
- Hypertrophy: increase in size of cells, resulting in an increase in size of organ
- Atrophy: shrinkage in size of cells
- Metaplasia: reversible change of one adult cell type(epithelial /mesenchymal) is replaced by another cell type.
- Dysplasia: disordered cellular development (also called atypical hyperplasia)

Both meta and hyperplasia are seen in this.

Hyperplasia

- Hyperplasia
  - Physiologic
    - Hormonal
    - Compensatory
  - Pathologic

Mechanism–

- Increased local production of growth factors
- Increased levels of growth factor receptor

→ Activation of particular intracellular signaling pathways

→ Production of transcription factors

→ Turn on many cellular genes that encode growth factors

→ Cellular proliferation

Hyperplasia classification

Physiologic		Pathologic
Hormonal Occurs with influence of hormones e.g. Hyperplasia of female breast at puberty, pregnancy and lactation Hyperplasia of pregnant uterus	*Compensatory* Hyperplasia occurs due to removal or damage of part of n organ e.g. Regeneration of liver following partial hepatectomy Regeneration of epidermis after skin abrasion	Due to excessive hormonal stimulation and growth factors acting on target cells e.g. Endometrial hyperplasia following oestrogen excess Formation of skin warts or lesions (hyperplasia of epidermis) due to papilloma virus

Hypertrophy

- Hypertrophy
  - Physiologic
  - Pathologic

Mechanism–1.

- Signal transduction pathways → Induction of new genes → Stimulate synthesis of numerous proteins → Increase organelle–mitochondria, ER, myofibrils. Increase synthesis of DNA & RNA

2.

- Early development genes re-expressed in hypertrophic cells

Product of these genes participate in cellular response to stress

Genes that are induced during hypertrophy include-

1. Encoding transcription factors
2. Growth factors
3. Vasoactive substances

Hypertrophy classification

Physiologic	Pathologic
Most common stimulus is work load. Work load is shared by greater mass of cellular components and each muscle fiber is spared excess work &so escapes injury e.g. Enlarged size of uterus in pregnancy(hormone induced hypertrophy) Hypertrophy of breast during lactation due to prolactin and estrogen.	Hypertrophy of cardiac muscle due to chronic hemodynamic overload, resulting from Hypertension Aortic valve disease (stenosis)

Atrophy

- Atrophy

Physiologic
Decrease of uterus size after parturition

Pathologic
Depends on underlying cause

Mechanism of atrophy

Results from

- Decreased protein synthesis
- Increased protein degradation

Due to decreased metabolic activity → Decreased protein synthesis

Mechanism of atrophy

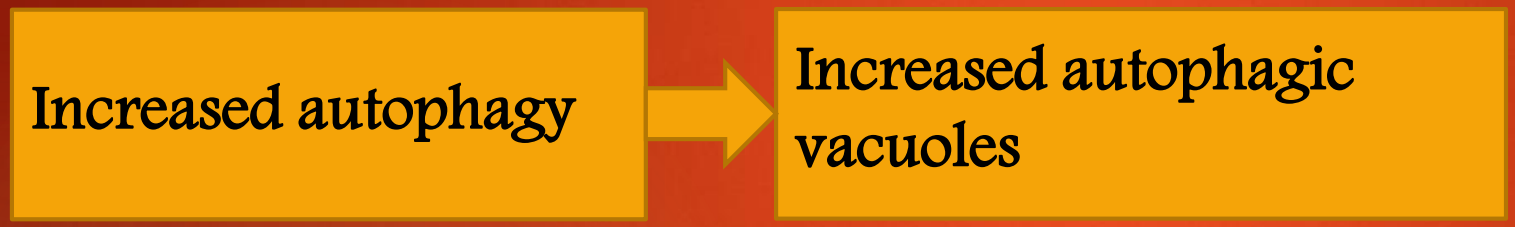
Protein degradation

1. Ubiquitin–protease pathway

Mechanism of atrophy

Protein degradation

2. Increased autophagy (self eating)



Autophagy: starved cells eats its own components to find nutrients and survive.

Causes of pathological atrophy

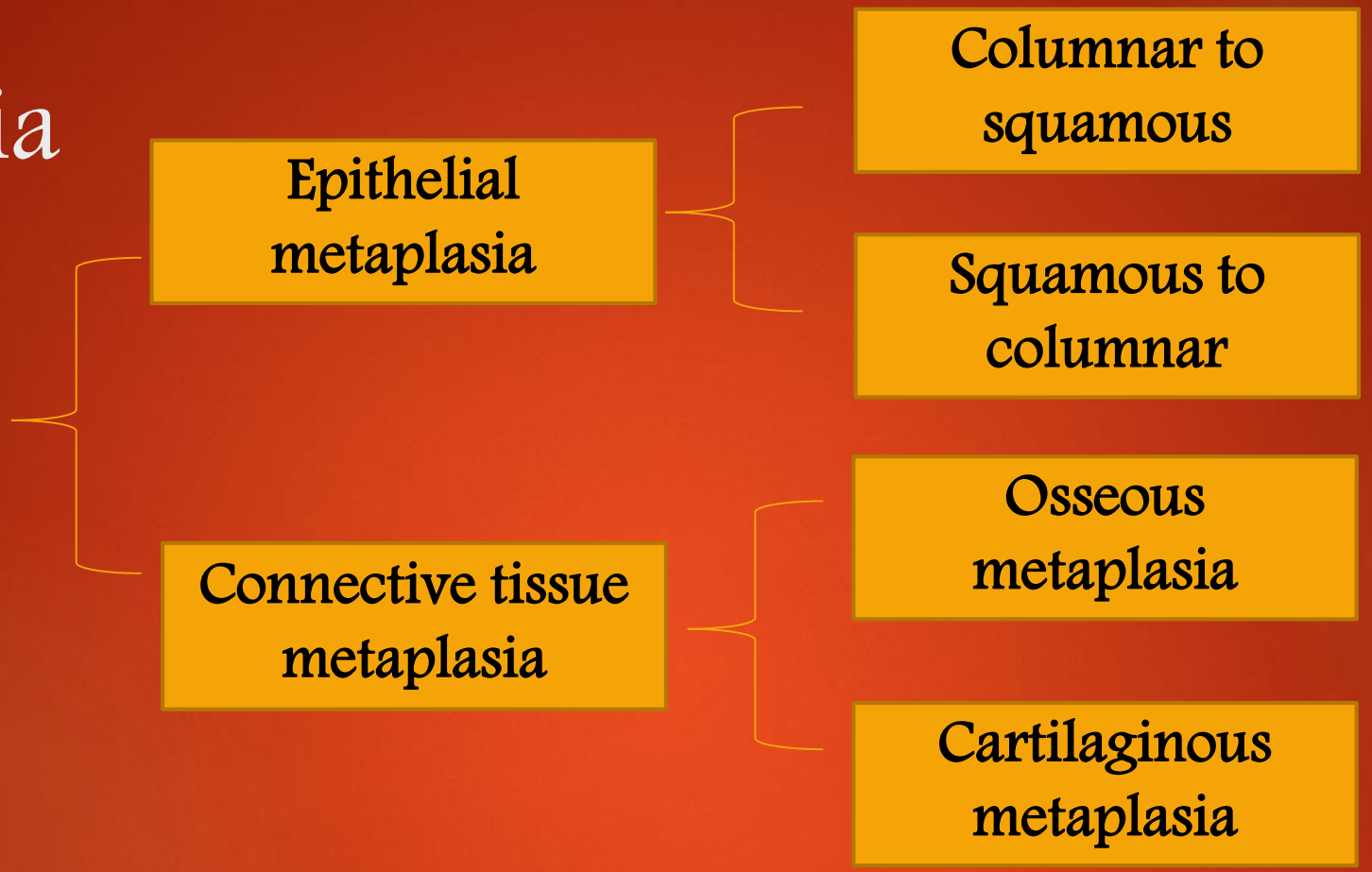
- Disuse atrophy–wasting or muscle atrophy in complete bed rest
- Denervation atrophy–rapid atrophy of muscle fibers due to damage of nerve which innervated them
- Ischemic atrophy–atrophy due to decreased blood supply to tissue (atrophy of brain in cerebral atherosclerosis)
- Inadequate nutrition /starvation atrophy–muscle wasting due to malnutrition (seen in cancer and chronic inflammatory disease)

Causes of pathological atrophy

- Endocrine atrophy–loss of endocrine stimulation leads to decreased metabolic activity of tissue (hypopituitarism may lead to atrophy of thyroid, adrenal & gonads)
- Pressure atrophy– Tissue compression for long time (enlarging benign tumor can cause atrophy in surrounding compressed tissues)
- Idiopathic atrophy– No obvious cause (e.g. myopathies, testicular atrophy)

Metaplasia

- Metaplasia



Mechanism of Metaplasia

Signals generated by cytokines, growth factors, extracellular matrix components

→

Reprogramming of stem cells

→

Metaplasia

Epithelial metaplasia

Columnar to squamous- In cigarette smoking ciliated epithelial cells of trachea & bronchi replaced by stratified squamous epithelial cells

In cholelithiasis-replacement of normal secretory columnar epithelium by non functioning stratified squamous epithelium.

Squamous to columnar

In barett esophagus squamous is replaced by intestine like columnar cells under the influence of refluxed gastric acid

Connective tissue metaplasia

Osseous metaplasia: Formation of cartilage, bone or adipose tissue (mesenchymal tissue) in tissues that generally don't contain them. Formation of bone in muscle in myositis ossificans.

Cartilaginous metaplasia: occurs where there is less mobility during the healing of fractures

In synovial chondromatosis, cells of the synovial membrane undergo metaplasia to become cartilage-producing chondrocytes. .

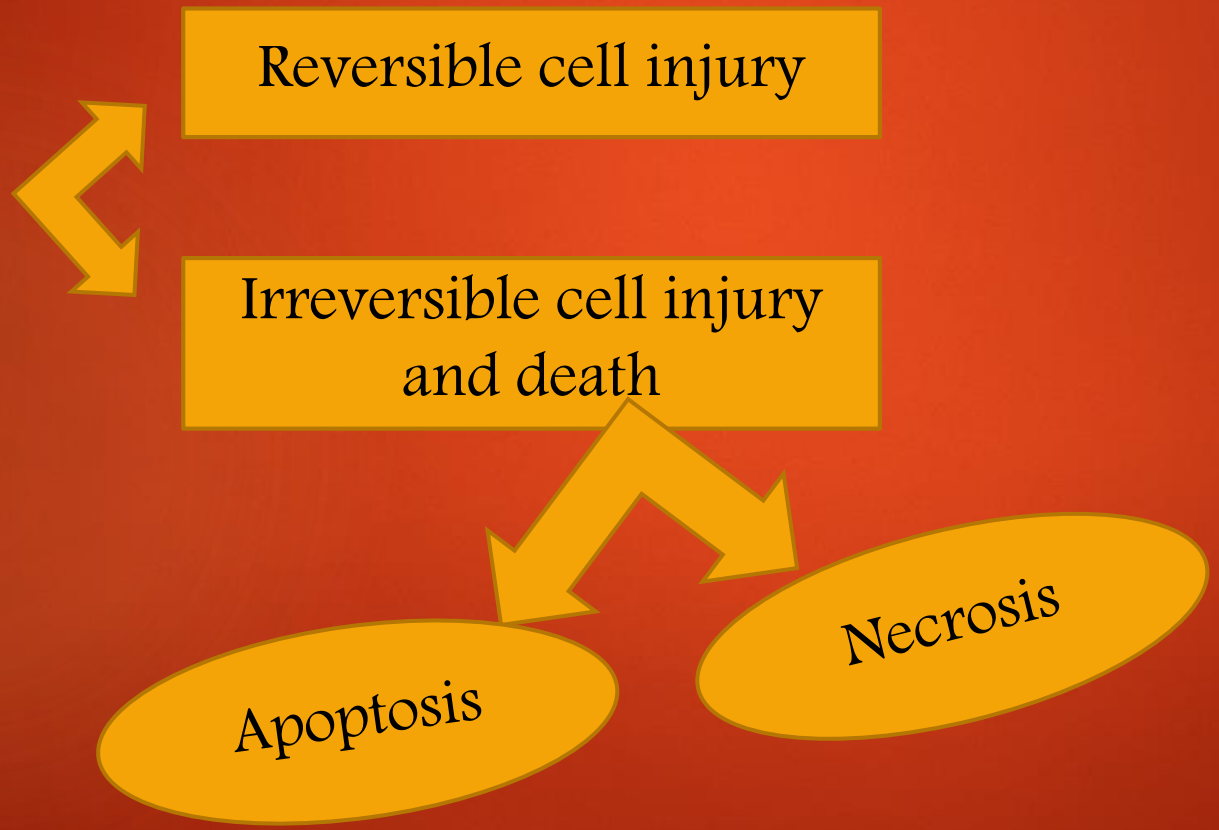
Dysplasia

- Disordered cellular development also called as atypical hyperplasia
- Both metaplasia and hyperplasia are seen
- Caused by chronic irritation and prolonged inflammation.
- Epithelial dysplasia of the cervix (cervical intraepithelial neoplasia – a disorder commonly detected by an abnormal pap smear)

Cell injury and death

- Results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents.

- Cell injury



Causes of cell injury

1. Oxygen deprivation
   - Hypoxia
   - Ischemia
2. Physical agents–
   - Mechanical trauma
   - Temperature extremes
   - Change in atmosphere pressure
   - Radiation
   - Electric shock
3. Chemical agents & drugs–
   - Poisons
   - Air pollution
   - Industrial hazards
   - Social stimuli
   - Therapeutic drugs

4. Infectious agents & immunologic rxn's–

Virus, fungi, bacteria parasites and anaphylactic rxn's

5. Genetic derangements

Enzymatic abnormalities
Variations in genetic make up

6. Nutritional imbalances

Nutritional excess

Nutritional deficiency

Mechanism of cell injury

Cell response to injury depends on

- Type of injury
- Its duration
- Severity

Consequences of cell injury depends on

- Type
- State
- Adaptability of injured cell

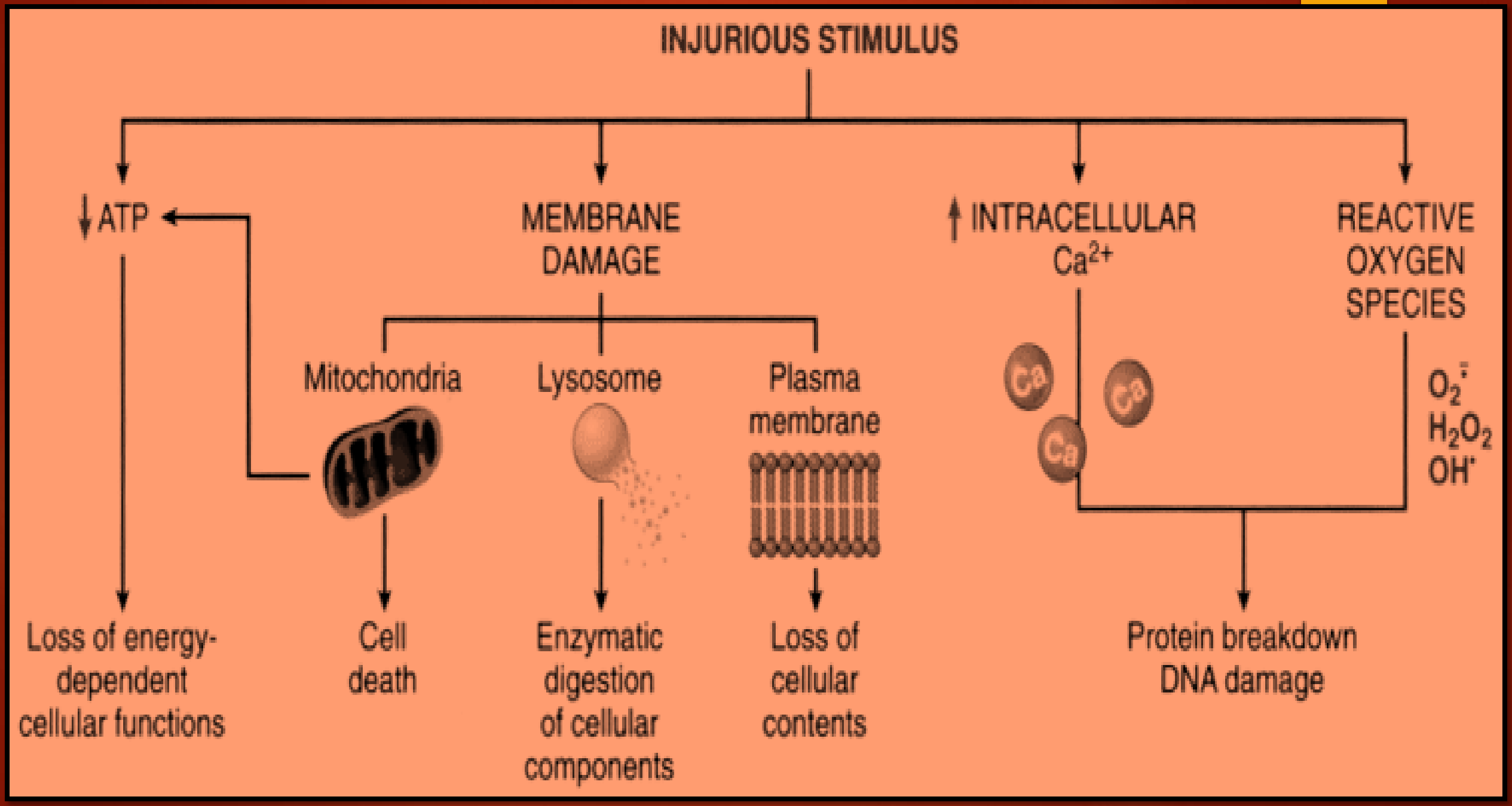
- Cell injury results from functional & biochemical abnormalities in one or more of several essential cellular components

Important targets of injurious stimuli

- Aerobic respiration (oxidative phosphorylation in mitochondria)
- Cell membrane integrity
- Protein synthesis
- Cytoskeleton
- Genetic apparatus integrity

Biochemical mechanisms responsible for cell injury

a) Depletion of ATP
b) Mitochondrial damage
c) Influx of intracellular Ca+2 & loss of Ca+2 homeostasis
d) Oxidative stress
e) Defects in membrane permeability.


INJURIOUS STIMULUS
ATP
MEMBRANE DAMAGE
INTRACELLULAR Ca^{2+}
REACTIVE OXYGEN SPECIES
Mitochondria
Lysosome
Plasma membrane
$O_2^{\cdot-}$
H_2O_2
$OH^{\cdot}$
Loss of energy-dependent cellular functions
Cell death
Enzymatic digestion of cellular components
Loss of cellular contents
Protein breakdown
DNA damage

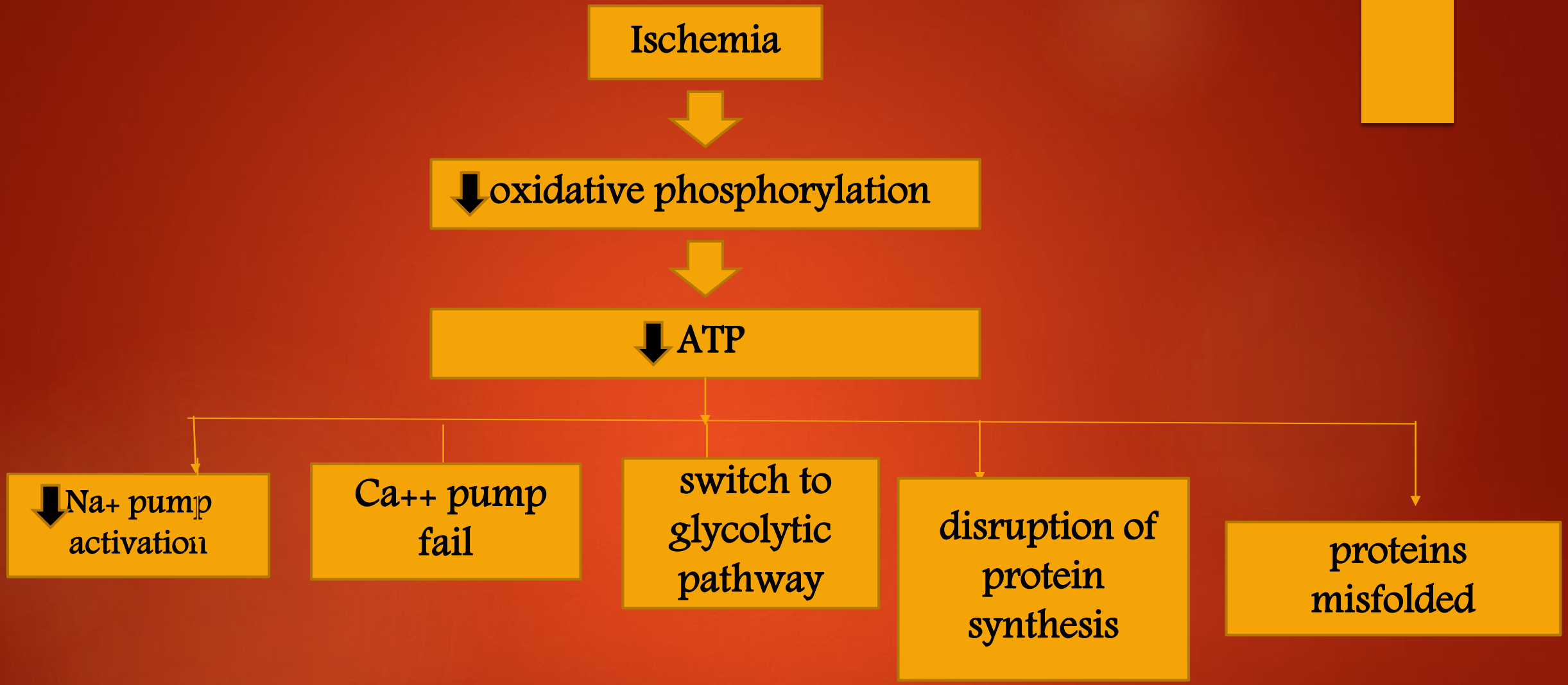
Depletion of ATP

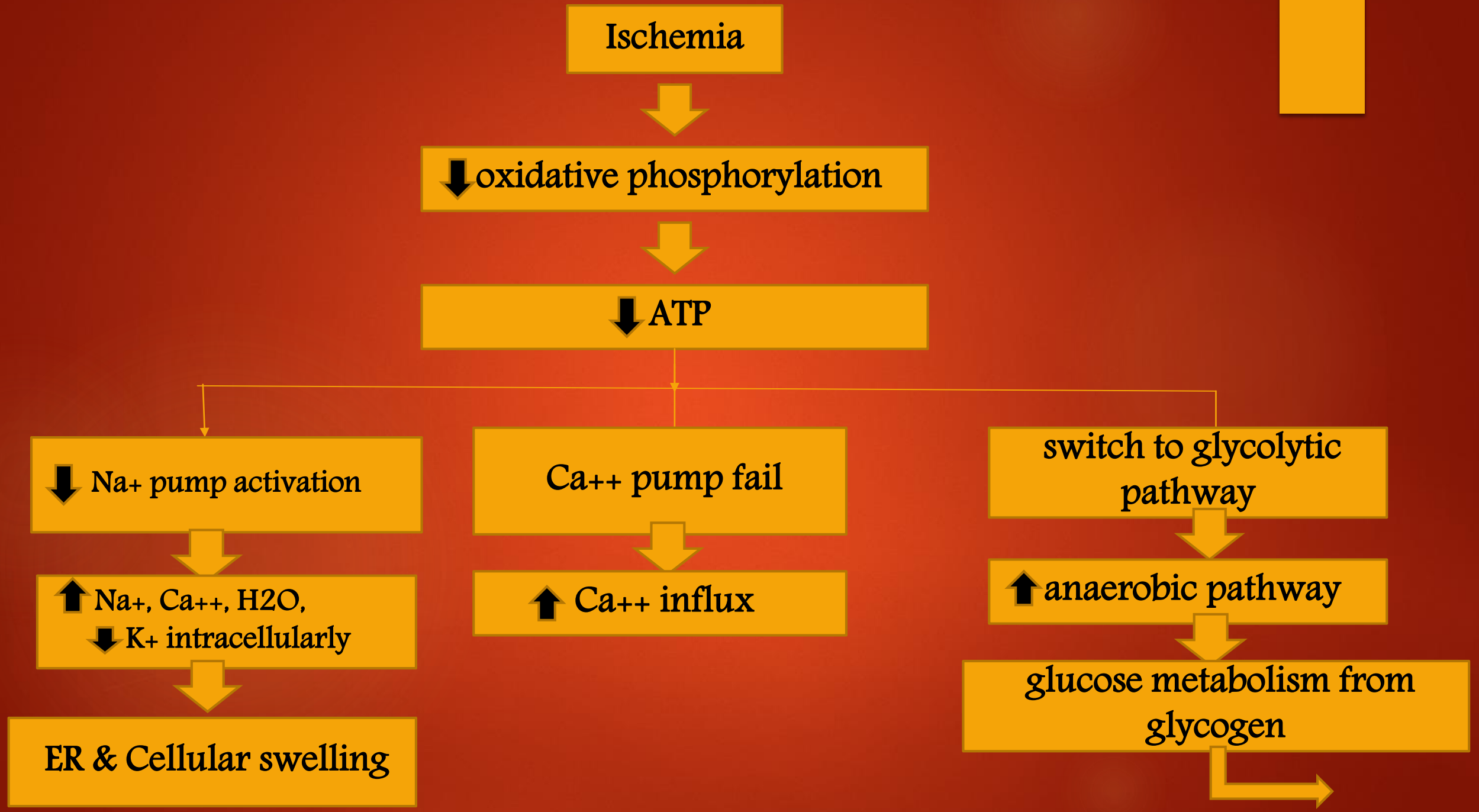
- ATP produced in 2 ways → **Oxidative phosphorylation**
  Glycolytic pathway

- Depletion of ATP is associated with both hypoxia and chemical stimuli

- ATP required for many synthetic & degradation process within the cell

- It involves in –membrane transport, protein synthesis, lipogenesis, deacylation & reacylation rxns, phospholipid turnover.


Ischemia
oxidative phosphorylation
ATP
Na+ pump activation
Ca++ pump fail
switch to glycolytic pathway
disruption of protein synthesis
proteins misfolded


Ischemia
oxidative phosphorylation
ATP
Na+ pump activation
Na+, Ca++, H2O,
K+ intracellularly
ER & Cellular swelling
Ca++ pump fail
Ca++ influx
switch to glycolytic pathway
anaerobic pathway
glucose metabolism from glycogen

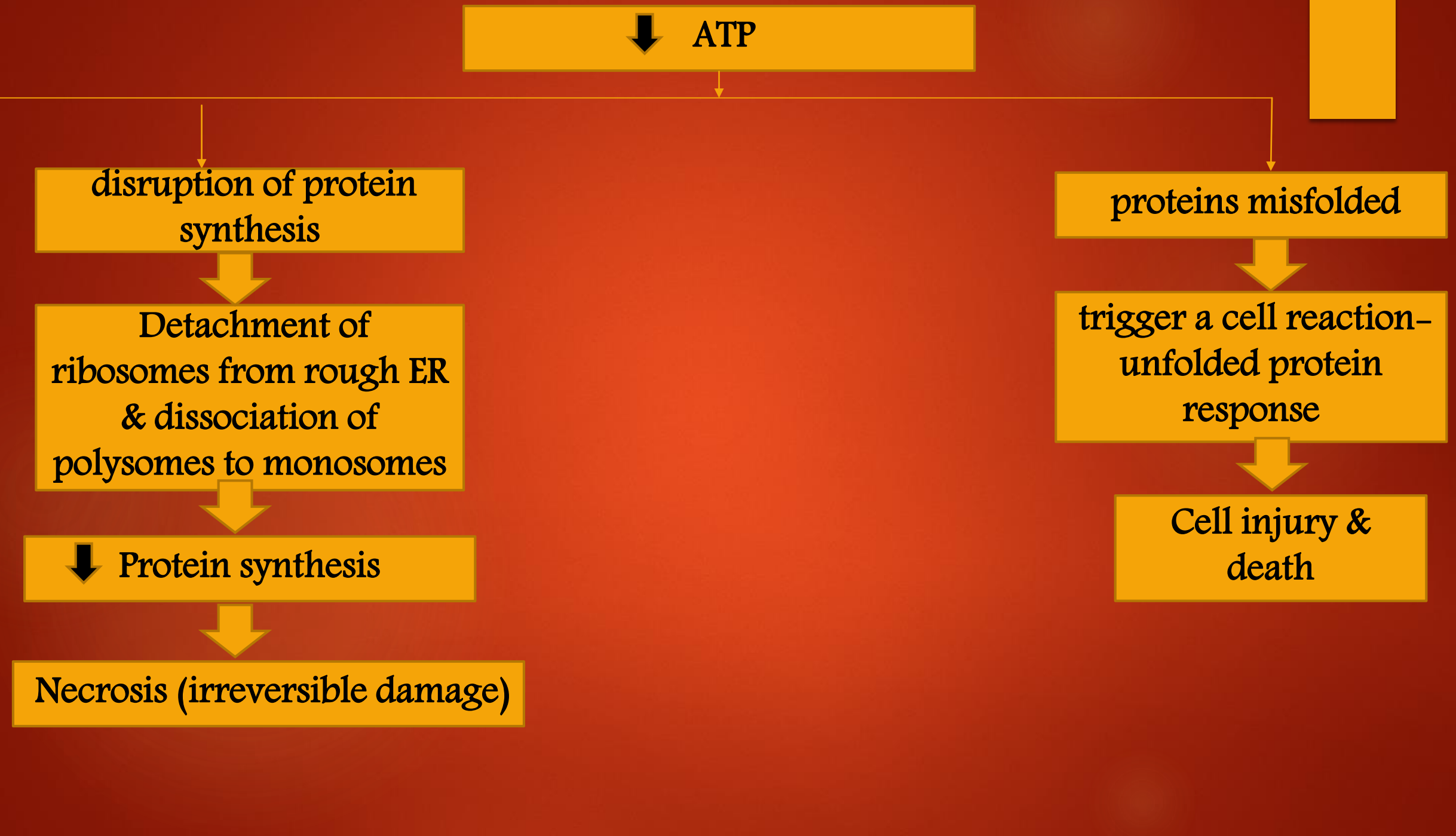
glucose metabolism from glycogen

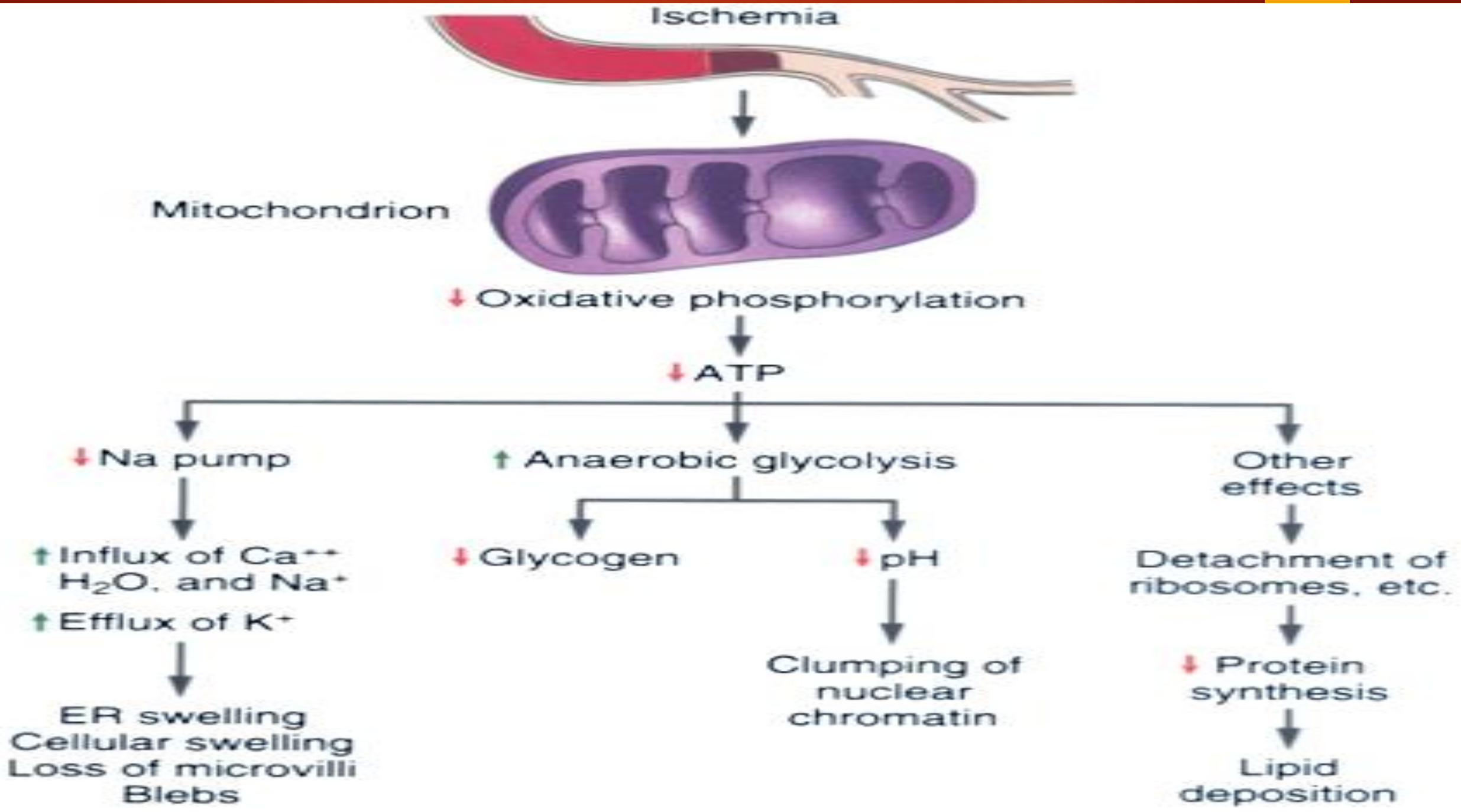
↓ glycogen(glycolysis)

accumulation of lactic acid & inorganic phosphates

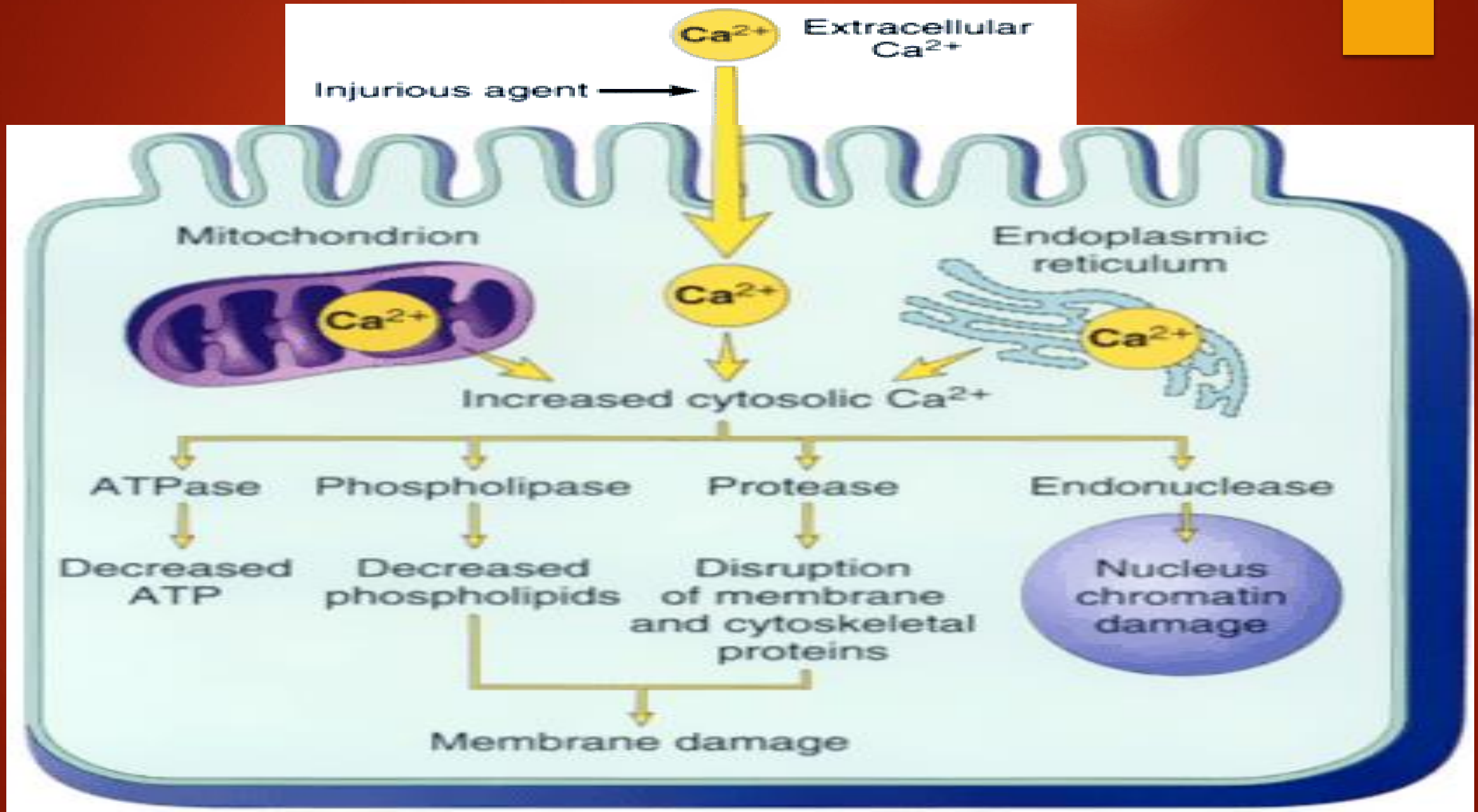
↓ PH

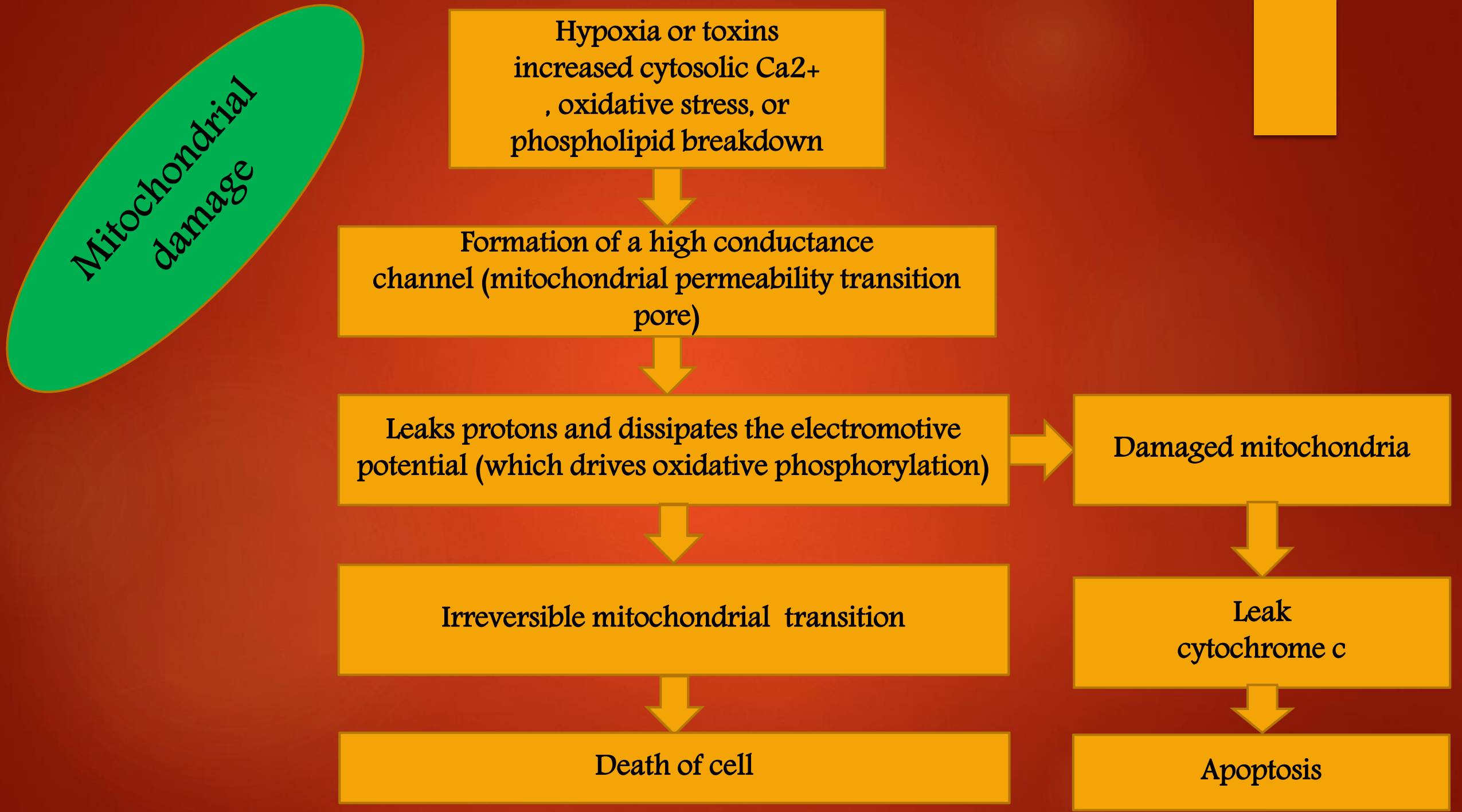
↓ activity of many cellular enzymes & clumping of nuclear chromatin


ATP
disruption of protein synthesis
Detachment of ribosomes from rough ER & dissociation of polysomes to monosomes
Protein synthesis
Necrosis (irreversible damage)
proteins misfolded
trigger a cell reaction- unfolded protein response
Cell injury & death

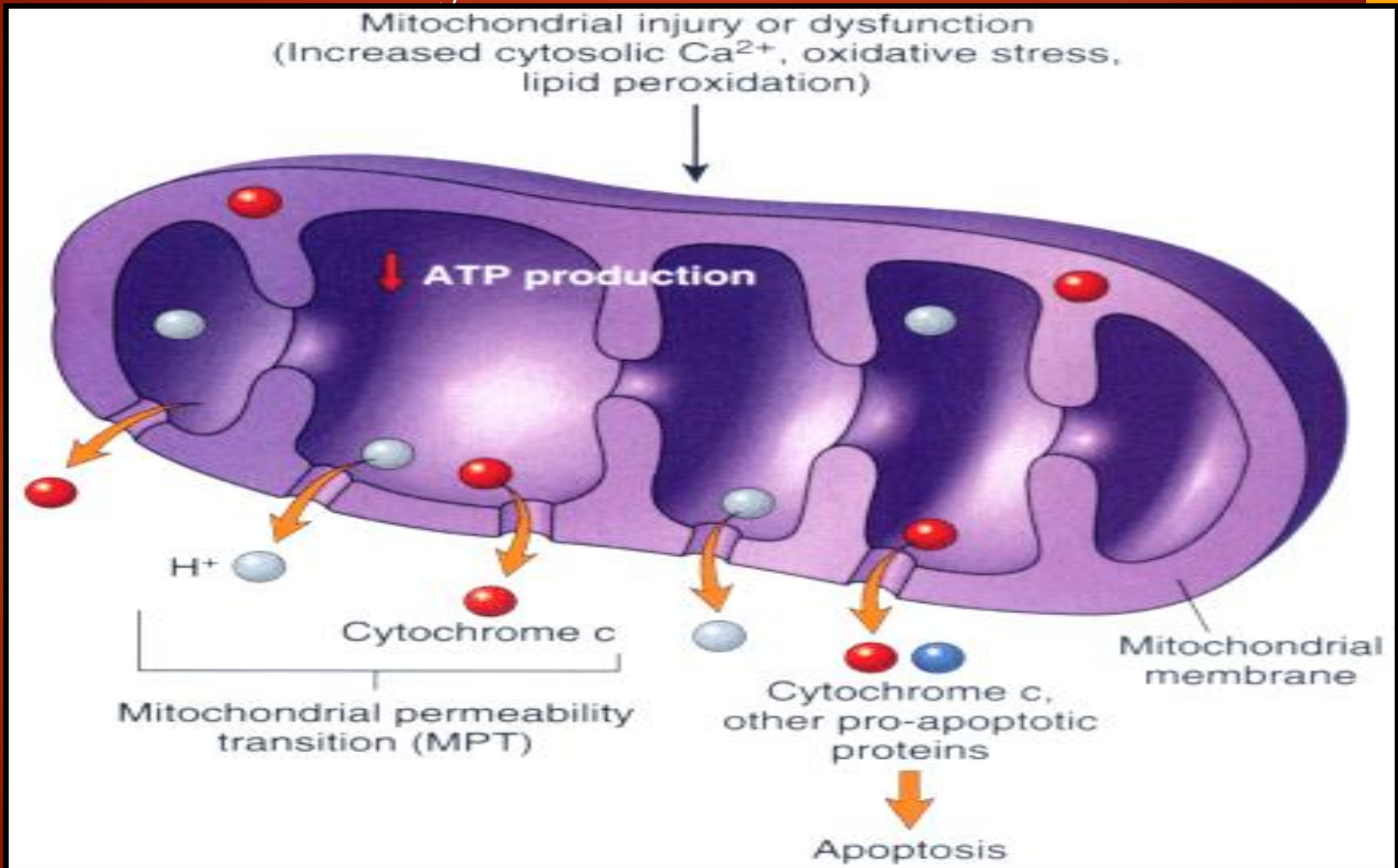

Ischemia
Mitochondrion
↓ Oxidative phosphorylation
↓ ATP
↓ Na pump
↑ Influx of Ca++ H2O, and Na+
↑ Efflux of K+
ER swelling
Cellular swelling
Loss of microvilli
Blebs
↑ Anaerobic glycolysis
↓ Glycogen
↓ pH
Clumping of nuclear chromatin
Other effects
Detachment of ribosomes, etc.
↓ Protein synthesis
Lipid deposition

Influx of intracellular calcium




Mitochondrial damage
Hypoxia or toxins
increased cytosolic Ca2+
, oxidative stress, or
phospholipid breakdown
Formation of a high conductance
channel (mitochondrial permeability transition
pore)
Leaks protons and dissipates the electromotive
potential (which drives oxidative phosphorylation)
Damaged mitochondria
Irreversible mitochondrial transition
Leak
cytochrome c
Death of cell
Apoptosis

Mitochondrial dysfunction



Oxidative stress

- Cell generate energy by reducing molecular oxygen to water

- During this process, small amounts of partially reduced reactive oxygen forms are produced as an unavoidable by product of mitochondrial respiration.

Some of these forms can damage

- Lipids
- Proteins
- Nucleic acids

- Imbalance between free radical generating and radical scavenging system results in oxidative stress.

- Free radicals initiate auto catalytic rxn's, where by molecules with which they react are themselves converted into free radicals to propagate the chain of damage.

Free radicals may be initiated within cells in several ways

- Absorption of radiant energy
- Enzymatic metabolism of exogenous chemicals or drugs
- The reduction-oxidation reactions that occur during normal metabolic processes
- Transition metals such as iron and copper donate or accept free electrons during intracellular reactions and catalyze free radical formation
- Nitric oxide (NO), an important chemical mediator can act as a free radical

Three reactions of reactive species are particularly relevant to cell injury

- Lipid peroxidation of membranes.
- Oxidative modification of proteins
- Lesions in DNA

Lipid peroxidation of membranes.

Double bonds in unsaturated fatty acids of membrane lipids are attacked by oxygen-derived free radicals

↓

Lipid–free radical interactions yield peroxides

↓

Peroxides
unstable and reactive

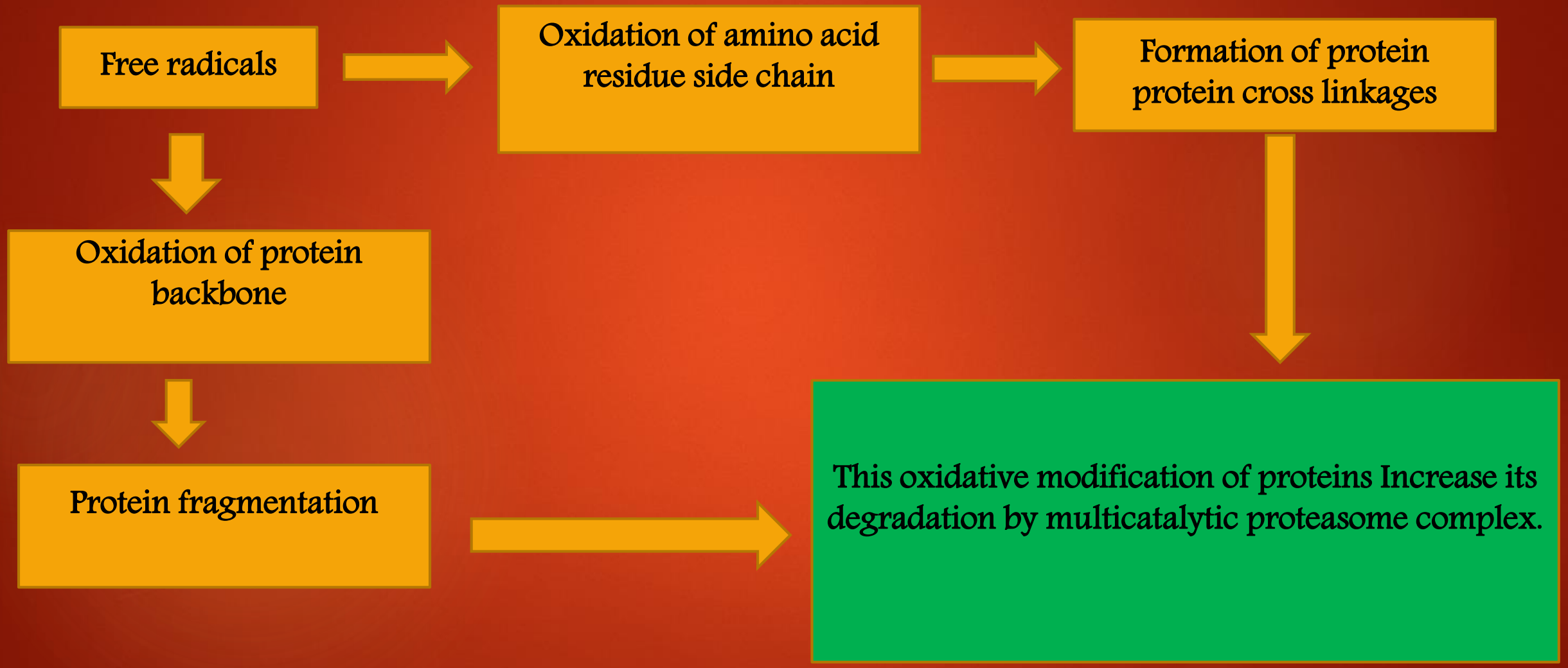
↓

Autocatalytic chain reaction ensues (called *propagation*)

↓

Extensive membrane, organelle, and cellular damage

Oxidative modification of proteins



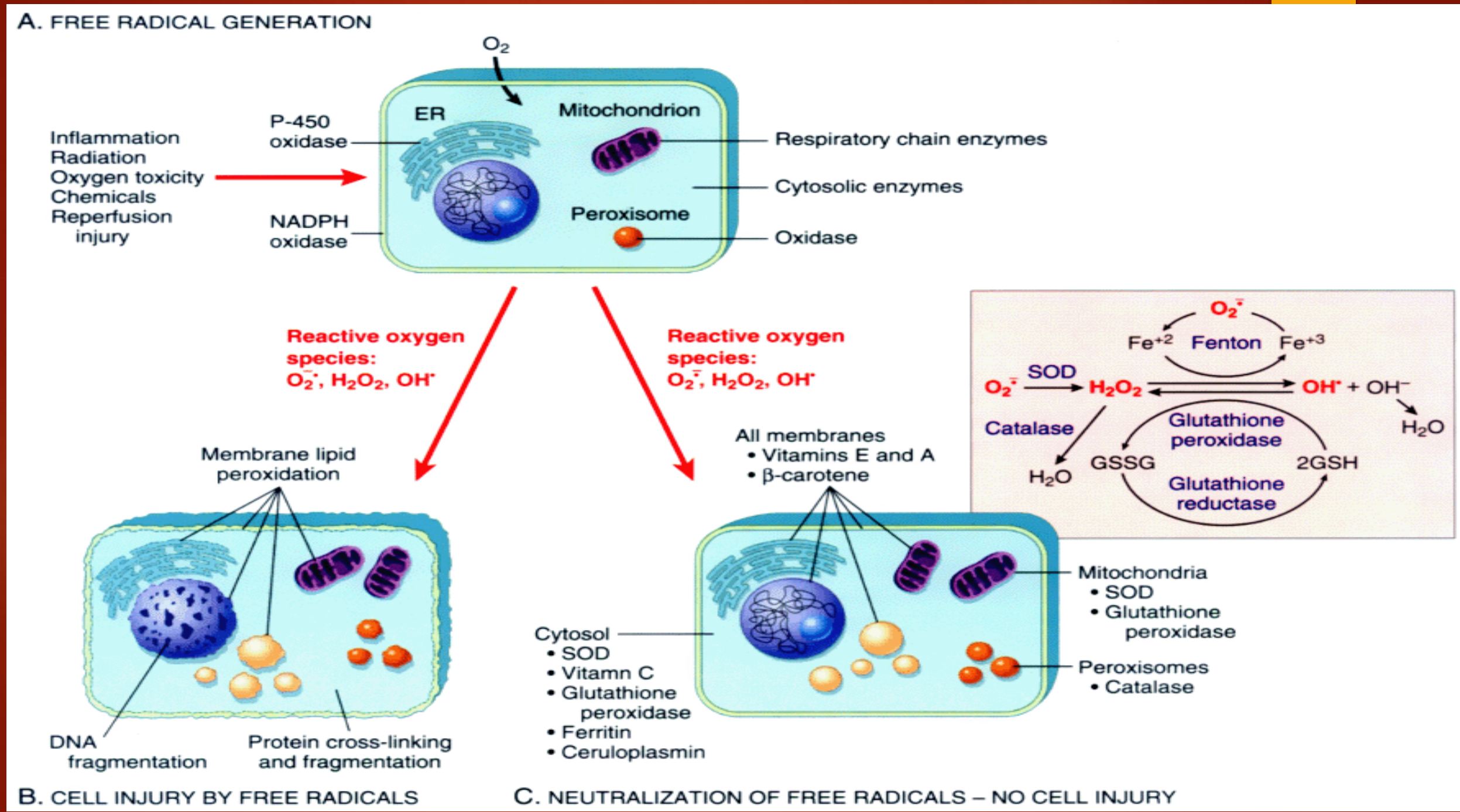
Lesions in DNA

Free Radicals React with thiamine in nuclear & mitochondrial DNA

Produce single stranded breaks in DNA

- Cells have developed multiple mechanisms to remove free radicals and thereby minimize injury.
- Free radicals are inherently unstable and generally decay spontaneously
- Several non enzymatic and enzymatic systems that contribute to inactivation of free radical reactions

- Antioxidants (non enzymatic)–Vit E & A, ascorbic acid, glutathione.
- Enzymes–catalase, superoxide dismutase, glutathione peroxidase.
- In many pathologic processes, the final effects induced by free radicals depend on the net balance between free radical formation and termination


A. FREE RADICAL GENERATION
O_2
ER
Mitochondrion
P-450 oxidase
Inflammation
Radiation
Oxygen toxicity
Chemicals
Reperfusion injury
NADPH oxidase
Peroxisome
Respiratory chain enzymes
Cytosolic enzymes
Oxidase
Reactive oxygen species:
$O_2^{-\cdot}$, H_2O_2, $OH^{\cdot}$
Reactive oxygen species:
$O_2^{-\cdot}$, H_2O_2, $OH^{\cdot}$
$O_2^{-\cdot}$
Fe^{+2} Fenton Fe^{+3}
SOD
$O_2^{-\cdot}$ → H_2O_2 ⇌ $OH^{\cdot}$ + OH^-
H_2O
Catalase
H_2O
GSSG
Glutathione peroxidase
2GSH
Glutathione reductase
Membrane lipid peroxidation
All membranes
• Vitamins E and A
• β-carotene
Mitochondria
• SOD
• Glutathione peroxidase
Peroxisomes
• Catalase
Cytosol
• SOD
• Vitamn C
• Glutathione peroxidase
• Ferritin
• Ceruloplasmin
DNA fragmentation
Protein cross-linking and fragmentation
B. CELL INJURY BY FREE RADICALS
C. NEUTRALIZATION OF FREE RADICALS – NO CELL INJURY

Membrane permeability defects

Bacterial toxins

Viral proteins

Lytic complement components

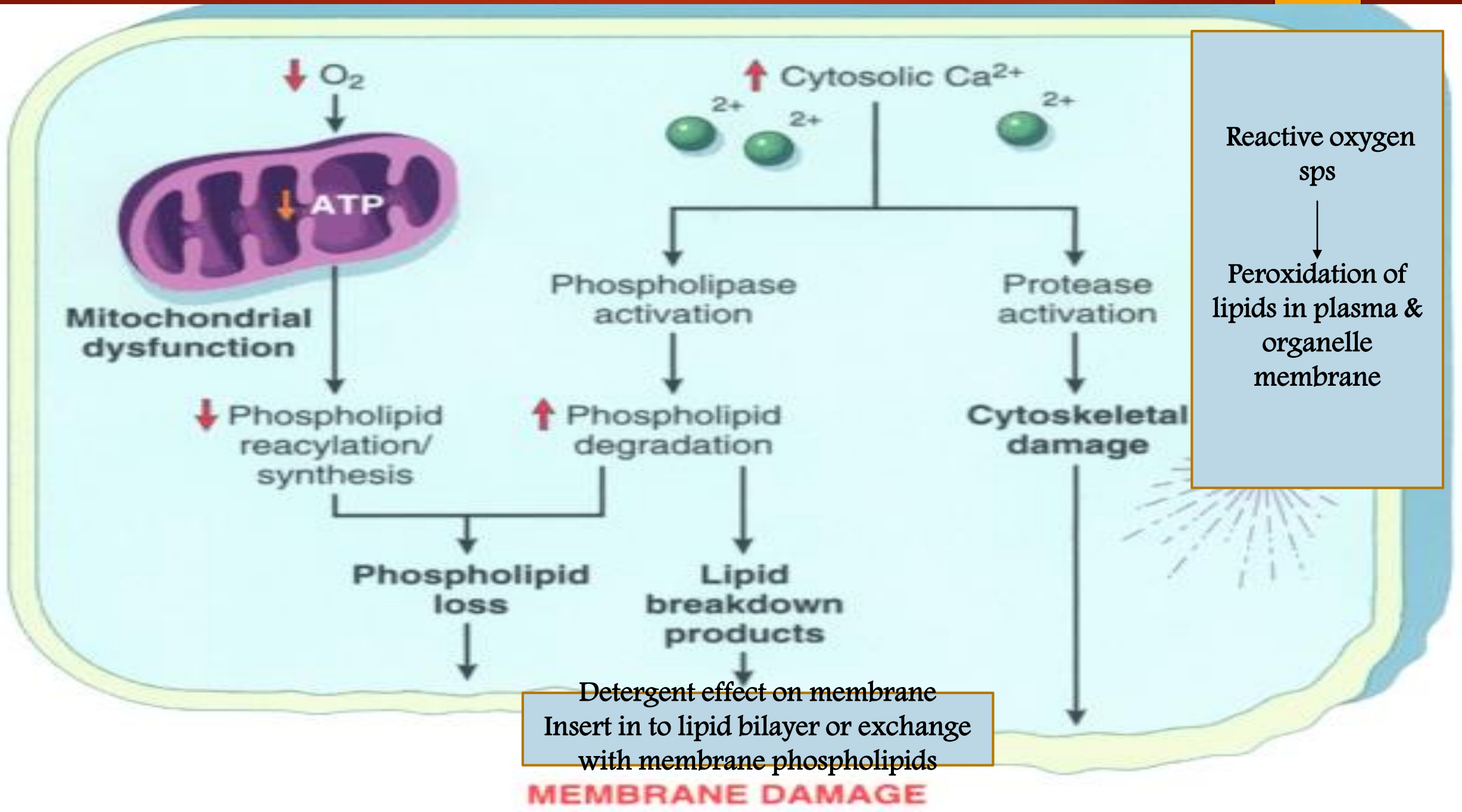
Physical & chemical agents

Directly

Damage plasma membrane

Others include

1. Mitochondrial dysfunction
2. Loss of membrane phospholipids
3. Cytoskeleton abnormalities
4. Reactive O2 species
5. Lipid break down products


O_2
ATP
Mitochondrial dysfunction
Cytosolic Ca^{2+}
2+
2+
2+
Phospholipase activation
Protease activation
Phospholipid reacylation/ synthesis
Phospholipid degradation
Cytoskeletal damage
Phospholipid loss
Lipid breakdown products
Detergent effect on membrane
Insert in to lipid bilayer or exchange with membrane phospholipids
MEMBRANE DAMAGE
Reactive oxygen sps
Peroxidation of lipids in plasma & organelle membrane

Consequences of loss of membranes

- Plasma membrane damage results in loss of osmotic balance and influx of fluids and ions, as well as loss of proteins, enzymes, coenzymes, and ribonucleic acids.

- The cells may also leak metabolites, which are vital for the reconstitution of ATP, thus further depleting net intracellular high-energy phosphates.

Consequences of loss of membranes

- Injury to lysosomal membranes results in leakage of their enzymes into the cytoplasm and activation of these enzymes.
- Lysosomes contain RNases, DNases, proteases, phosphatases, glucosidases, and cathepsins.
- Activation of these enzymes leads to enzymatic digestion of cell components, resulting in loss of ribonucleoprotein, deoxyribonucleoprotein, and glycogen, and the cells die by necrosis.

Reversible and Irreversible Cell Injury

- Persistent or excessive injury, however, causes cells to pass the threshold into irreversible injury

Two phenomena consistently characterize irreversibility.

- Inability to reverse mitochondrial dysfunction (lack of oxidative phosphorylation and ATP generation)

- Profound disturbances in membrane function.

Whatever the mechanism(s) of membrane damage, the end result is

- Massive leak of intracellular materials and
- A massive influx of calcium

Morphology of Reversible injury

Two patterns of reversible cell injury (seen under the light microscope)

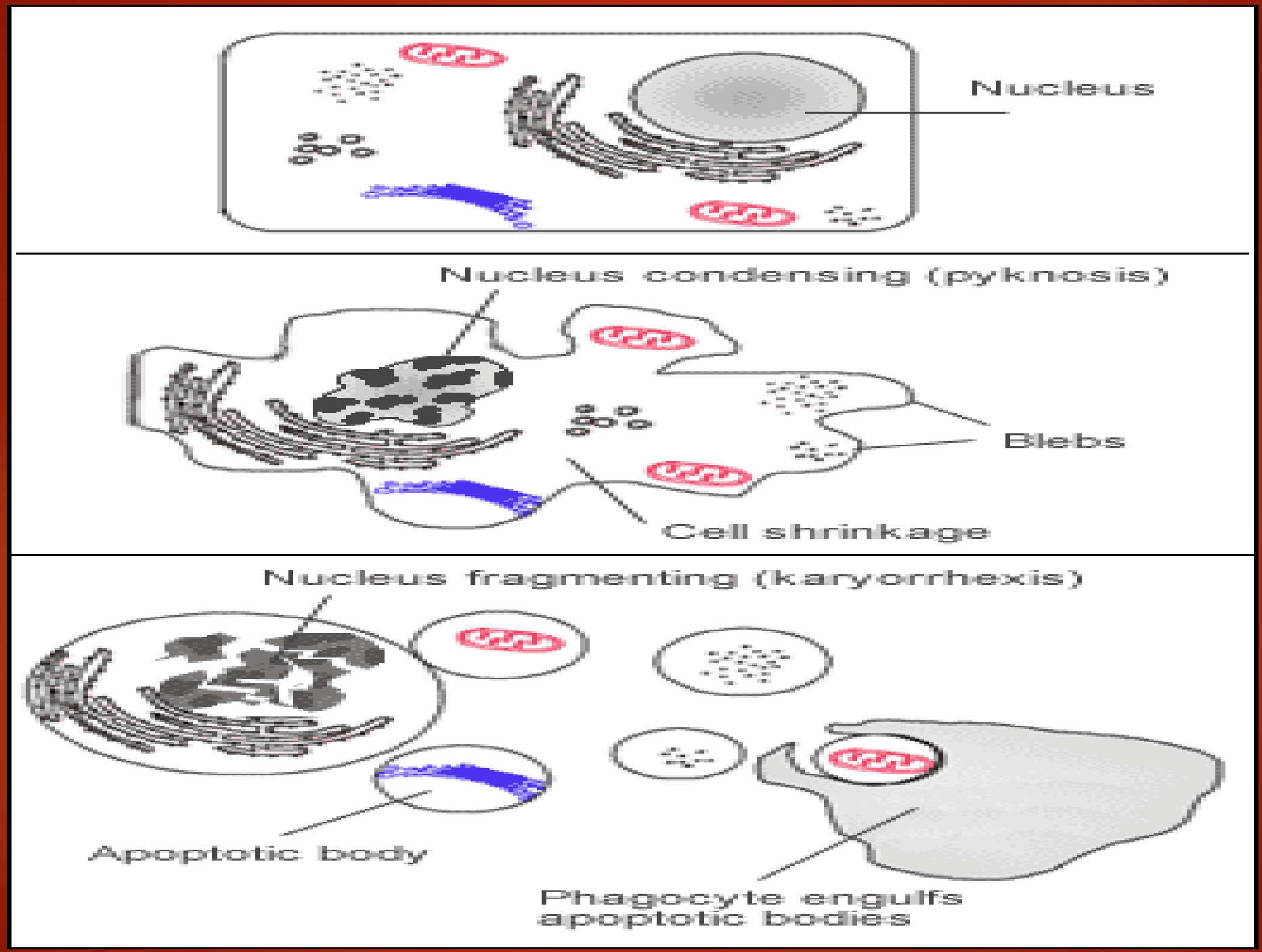
- Cellular swelling and
- Fatty change

- Plasma membrane alterations, such as blebbing, blunting, and distortion of microvilli; creation of myelin figures; and loosening of intercellular attachments

- Mitochondrial changes, including swelling, rarefaction, and the appearance of small phospholipid-rich amorphous densities

- Dilation of the endoplasmic reticulum, with detachment and disaggregation of polysomes

- Nuclear alterations, with disaggregation of granular and fibrillar elements.


Nucleus
Nucleus condensing (pyknosis)
Blebs
Cell shrinkage
Nucleus fragmenting (karyorrhexis)
Apoptotic body
Phagocyte engulfs
apoptotic bodies

Necrosis

- Necrosis refers to a spectrum of morphologic changes that follow cell death in living tissue, largely resulting from the progressive degradative action of enzymes on the lethally injured cell.

- Necrotic cells are unable to maintain membrane integrity and their contents often leak out

- The morphologic appearance of necrosis is the result of denaturation of intracellular proteins and enzymatic digestion of the cell.

- Ultimately, in the living patient, most necrotic cells and their debris disappear by a combined process of enzymatic digestion and fragmentation, followed by phagocytosis of the particulate debris by leukocytes

- If necrotic cells and cellular debris are not promptly destroyed and reabsorbed, they tend to attract calcium salts and other minerals and to become calcified. This phenomenon, called dystrophic calcification

Morphology of necrosis

Necrotic cells show

- Increased eosinophilia
- Glassy homogenous appearance (due to glycogen loss)
- Moth-eaten appearance of cytoplasm (digested cytoplasm)
- Calcification
- Replacement by phospholipid masses (myelin figures)
- Dilation of mitochondria with large amorphous densities
- Amorphous osmiophilic debris
- Discontinuities in plasma and organelle membranes
- Aggregates of fluffy material probably representing denatured protein

Nuclear change

- Karyolysis (basophilia of chromatin fade)
- Pyknosis (nuclear shrinkage & increased basophilia)
- Karyorrhexis (pyknotic nucleus undergo fragmentation)

Types of necrosis

- Coagulative necrosis
- Liquefactive necrosis
- Caseous necrosis
- Fat necrosis

Examples of cell injury and necrosis

- ??????????????????

Apoptosis

- Programmed cell death
- Pathway of cell death that is induced by a tightly regulated intracellular program in which cells destined to die by activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins
- In apoptosis dead cells rapidly cleared before its contents leaked out
- Apoptosis occurs when cells are damaged beyond repair (esp when DNA affected)

It occurs in

1. Pathological conditions

- Cell death produced by a variety of injurious stimuli
- Cell death in tumors

2. Physiological conditions

- Cell death induced by cytotoxic T cells, a defense mechanism
- Hormone-dependent involution in the adult, such as endometrial cell breakdown during the menstrual cycle

Mechanism of apoptosis

Divided into two phases

- Initiation phase- Capases become catalytically active

- Execution phase-Capases act to cause cell death.

Initiation phase

Acts by 2 pathways

- Extrinsic or receptor mediated pathway
- Intrinsic or mitochondrial pathway

Execution phase

- Procaspases get activated (executor caspase) by caspase 8 0r 10 in extrinsic pathway or by caspase 9 in intrinsic pathway
- Executor caspase formed will further give +ve feed back to produce massive of active caspases
- This leads to activation of death program in which the activated caspases act on many cellular components (cleave cytoskeleton ,nuclear protein, breakdown of nuclear matrix) resulting in cell death.

Removal of dead cells

- Dying cells secrete soluble factors which recruit phagocytes
- Apoptotic cells have marker molecules on surface which facilitate early recognition by adjacent cells/phagocytes.
- Macrophages secrete substance which specifically binds to dead cells

Morphology of cell undergoing apoptosis

- Cell shrinkage
- Chromatin condensation, nucleus break down
- Cytoplasmic blebs
- Apoptotic bodies
- Phagocytosis of apoptotic cells or cell bodies by macrophages

Biochemical features

- Protein cleavage
- DNA breakdown
- Phagocytic recognition