PATHOGENESIS OF CEREBRAL INFARCTION

Color index:

- Important
- Extra explanation

"FAILURE IS NOT FALLING DOWN BUT REFUSING TO GET UP"

Check this link before studying to know if there is any corrections in the teamwork

OBJECTIVES:

By the end of this lecture, the students should be able to:

- Identify the possible cell death mechanisms implicated in the pathogenesis of ischemic brain injury
- Acquire the knowledge of the important role played by oxidative stress and free radicals in the pathogenesis of cerebral infarction
- Understand the various factors involved in ischemia-induced metabolic stress
- Identify the Neurochemical changes involved in cerebral ischemia

Stroke

Hemorrhagic
Global incidence: 32%

- Intracerebral
- Subarachnoid

Ischemic
Global incidence: 68%

- Thrombotic
- Embolic

- **Hemorrhagic:** rupture of blood vessel (leakage)
- Intracranial & Subarachnoid differ in location
- **Intracranial**: Inside the brain

Subarachnoid: in the surface of Blood vessel, usually the patient complain with severe headache (worst headache in life)

Cerebral ischemia: loss of blood supply to part of the brain

- ➢ less o2 , less glucose
- ➢ death of tissue

-Thrombotic: clot "block" in the vessel of the brain. Ex: cholesterol plaque.

-Embolic: plaque travel from another place, it's usually heard.

Brain hemorrhage

Risk Factors of Strokes

- Some increase the risk of one type of stroke (hemorrhagic or ischemic).
- Some increase the risk of both types.
- Occasionally, strokes occur in people who have no risk factors.

*Men are more prone in general and old Age women.
***Transient ischemic attack**: mini stroke, doesn't cause irreversible damage, short time, no radiological evidence.
Diagnosis: based on symptoms.
***Classic stoke symptoms**:
-Face drooping
-Arm weakness
-Speech Slurred
-Time counts (call an ambulance).

Risk factors of strokes

Ischemic stroke risk factors

-Age older than 40 years.
-Heart disease, Hypertension & Hypercholesterimea.
-Smoking Diabetes& Illegal drug use.
-Recent childbirth.
-Previous history of transient ischemic attack.
-Inactive lifestyle and lack of exercise & Obesity.
-Current or past history of blood clots.
-Family history of cardiac disease and/or stroke.

Hemorrhagic stroke risk factors

-High blood pressure.
-Smoking.
-Illegal drug use (especially cocaine and "crystal meth").
-Use of warfarin or other blood thinning medicines.

Cell Death Mechanisms Implicated In The Pathogenesis of Ischemic Brain Injury

Cell death mechanisms in cerebral ischemia:

- **Necrosis** is commonly observed early after severe ischemic insults.
- **Apoptosis** occurs with more mild insults and with longer survival periods.

Difference :

1- Necrosis: unprogrammed event by injury, trauma, any external stimuli.

2- Apoptosis: programmed event (life span over) macrophages start the processes which has the apoptotic enzyme.

-The mechanism of cell death involves calcium-induced calpain-mediated proteolysis of brain tissue.

-Substrates for calpain include: Cytoskeletal proteins, Membrane proteins and Regulatory and signaling proteins.

Biochemical Responses To Ischemic Brain Injury

- Oxidative stress.

excess production of free radical is harmful why? They have free electron which means high chemical activity.

- Metabolic stress.

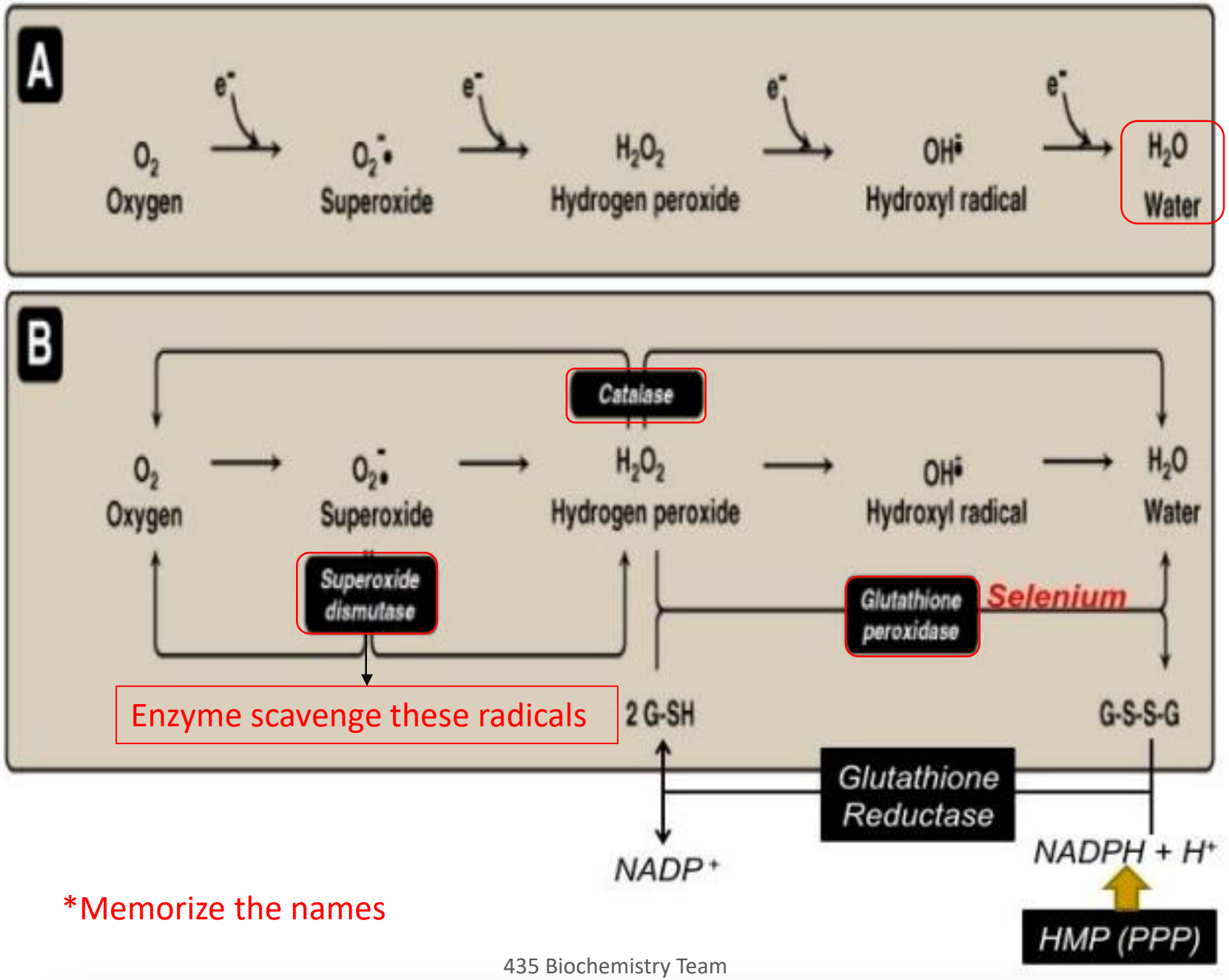
less o2 , less glucose leads to less ATP (energy).

- Neurochemical response.

1.Oxidative Stress:

The Role Of Reactive Oxygen Species (ROS) & Reactive Nitrative Species (RNS) In Normal Brain Physiology

- They are mainly generated by microglia & astrocytes.
- They modulate synaptic transmission & non-synaptic communication between neurons & glia.
- During periods of increased neuronal activity, ROS & RNS diffuse to the myelin sheath of oligodendrocytes activating Protein kinase C (PKC)⇨posttranslational modification of myelin basic protein in myelin sheath (MBP) by phosphorylation.
- They regulate neuronal signaling in both central & peripheral nervous systems.
- They are required for essential processes as learning & memory formation.



*Memorize the names

Oxidative Stress

- A condition in which cells are subjected to excessive levels of Reactive oxidizing species (ROS or RNS) & they are unable to counterbalance their deleterious effects with antioxidants. (Imbalance between oxidants (⇧)and antioxidants(⇩))

  *Examples of antioxidants: enzyme, Vitamin A, Vitamin E.

- It has been implicated in the ageing process & in many diseases (e.g., atherosclerosis, cancer, neurodegenerative diseases, stroke).

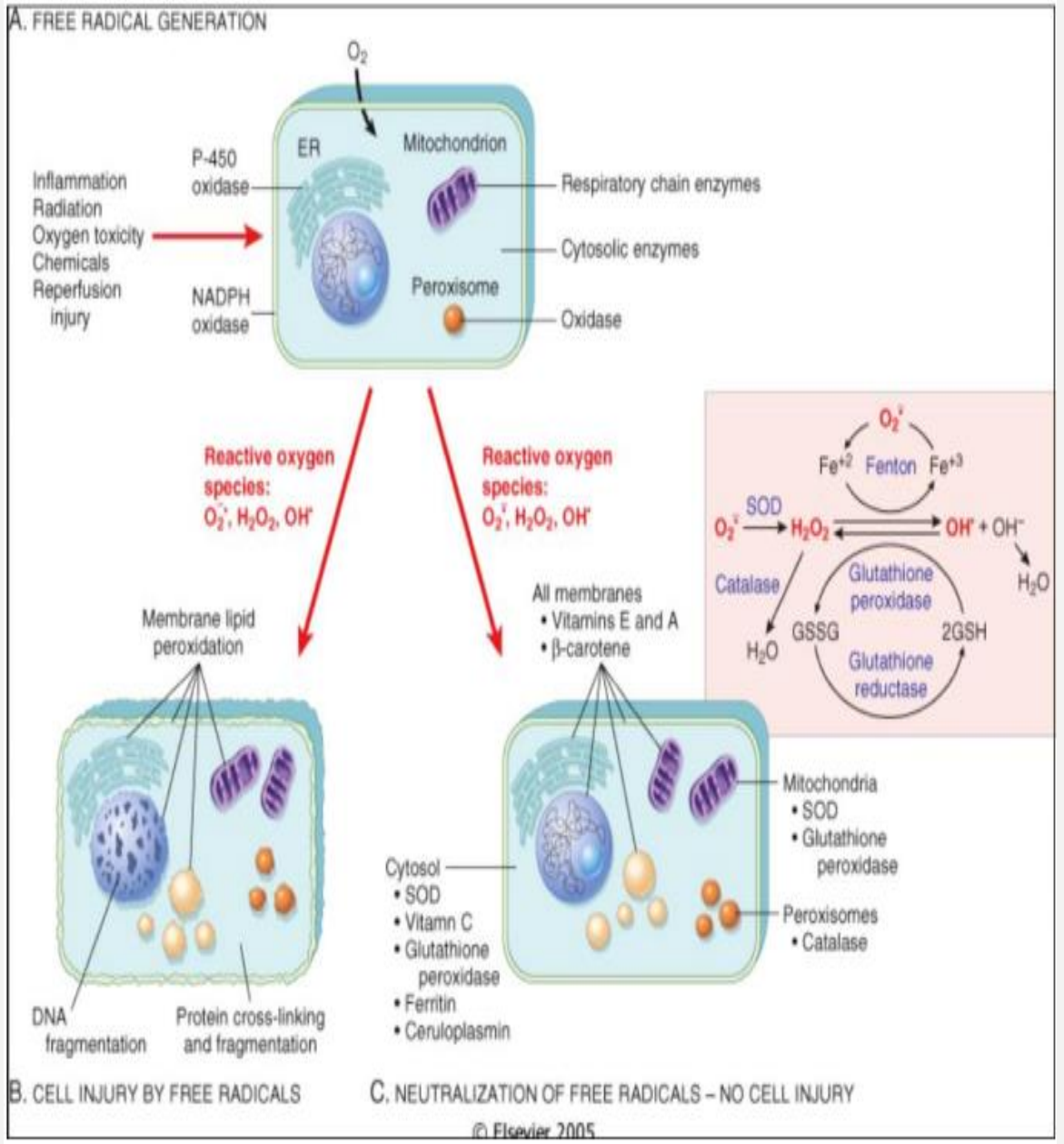
The brain and Oxidative stress:

***Neuron > less ATP >parts depend on ATP (NA-K Pump) FAILS > build up of NA inside cell > increase ca in neuron > k thrown out of cell > Swelling (NA mainly) > Inflammation**

The brain is highly susceptible to ROS-induced damage because of:

- High concentrations of peroxidisable lipids.
- Low levels of protective antioxidants.
- High oxygen consumption.*more amount of free radicals.
- High levels of iron (acts as pro-oxidants under pathological conditions).
- The occurrence of reactions involving dopamine & Glutamate oxidase in the brain. *Excess Ca > dopamine and glutamate >increase influx of Ca > hyper excited state = Neurotoxic.

When antioxidants cannot counterbalance oxidants, oxidants (ROS) react with DNA, lipids and proteins producing harmful effects mentioned in the next slide.



Molecular & Vascular Effects of ROS In Ischemic Stroke

Molecular effects

-DNA damage (important).

-Lipid peroxidation of unsaturated fatty acids.

-Protein denaturation.

-Inactivation of enzymes.

-Cell signaling effects (e.g., release of Ca2+ from intracellular stores(mitochondria and Smooth endoplasmic reticulum)).

-Cytoskeletal damage.

-Chemotaxis.

Vascular effects

-Altered vascular tone (dilation) and decreased cerebral blood flow.

-Increased platelet aggregability.

-Increased endothelial cell permeability.

The Role Of NO In The Pathophysiology of Cerebral Ischemia

*Memorize the names

Ischemia results in: abnormal Nitric Oxide production

*This may be both beneficial and detrimental, depending upon when and where NO is released

*NO is produce by : endothelium derived endodilator.

Beneficial

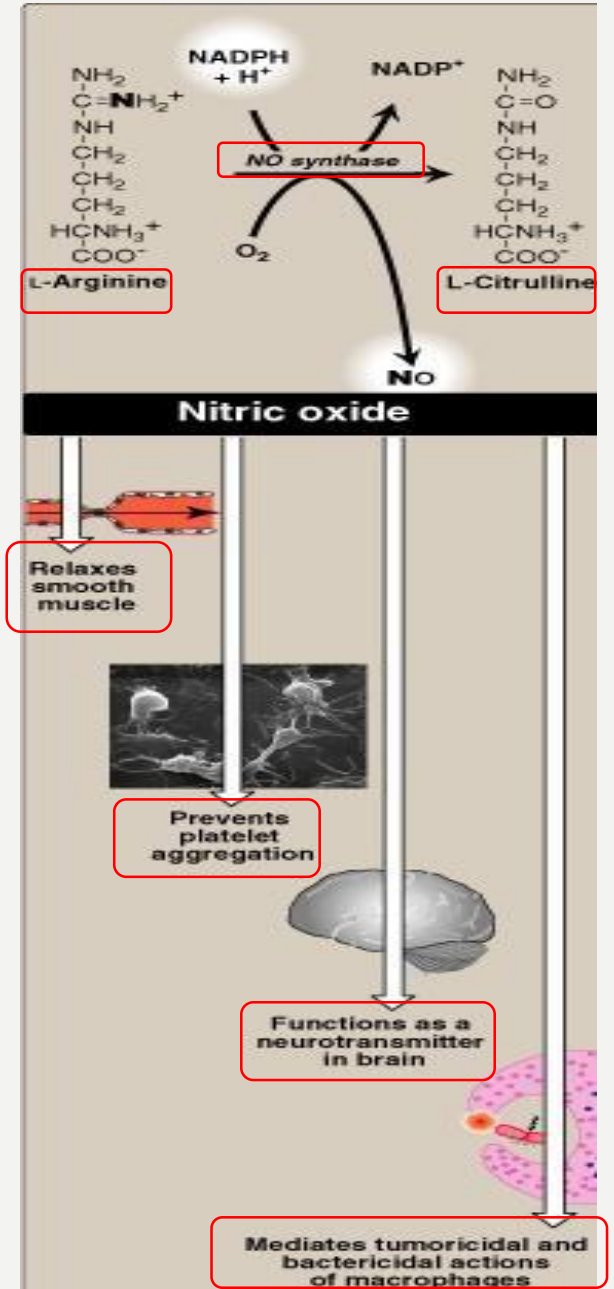
NO produced by endothelial NOS (eNOS) improves vascular dilation and perfusion

Harmful (detrimental)

NO production by neuronal NOS (nNOS) or by the inducible form of NOS (iNOS).
iNos has a similar effect to ROS

Increased iNOS activity generally occurs in a delayed fashion after brain ischemia and trauma and is associated with inflammatory processes

An increase of NO in macrophages may induce apoptosis.



2. Metabolic Stress

Ischemia → interruption or severe reduction of blood flow, O_2 & nutrients in cerebral arteries → energy depletion (depletion of ATP & creatine phosphate)

*Creatine phosphate: is a high energy compound that produce ATP by giving phosphate to ADP.

- Inhibition of ATP-dependent ion pumps
- Membranes depolarization
- Perturbance of transmembrane ion gradients

↑ **Lactic acid** in neurons →

Acidosis ↑H_2 → promotes the pro-oxidant effect → ↑ the rate of conversion of $O_2^{\cdot -}$ to H_2O_2 or to hydroxyperoxyl radical.

hydroxyperoxyl radical: HO_2 it's a free radical.

Ca^{+2} Influx (translocation from extracellular to intracellular spaces) →activation of cellular proteases (Calpains) & lipases → breakdown of cerebral tissue

Na^+ influx

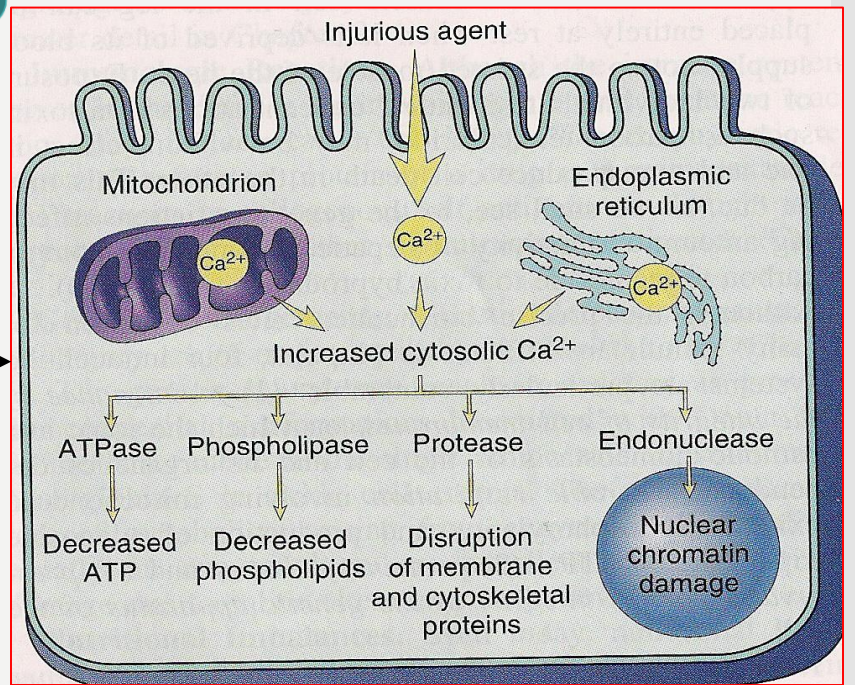
K^+ efflux

K+ induced release of excitatory amino acids

*Na^+ influx causes edema

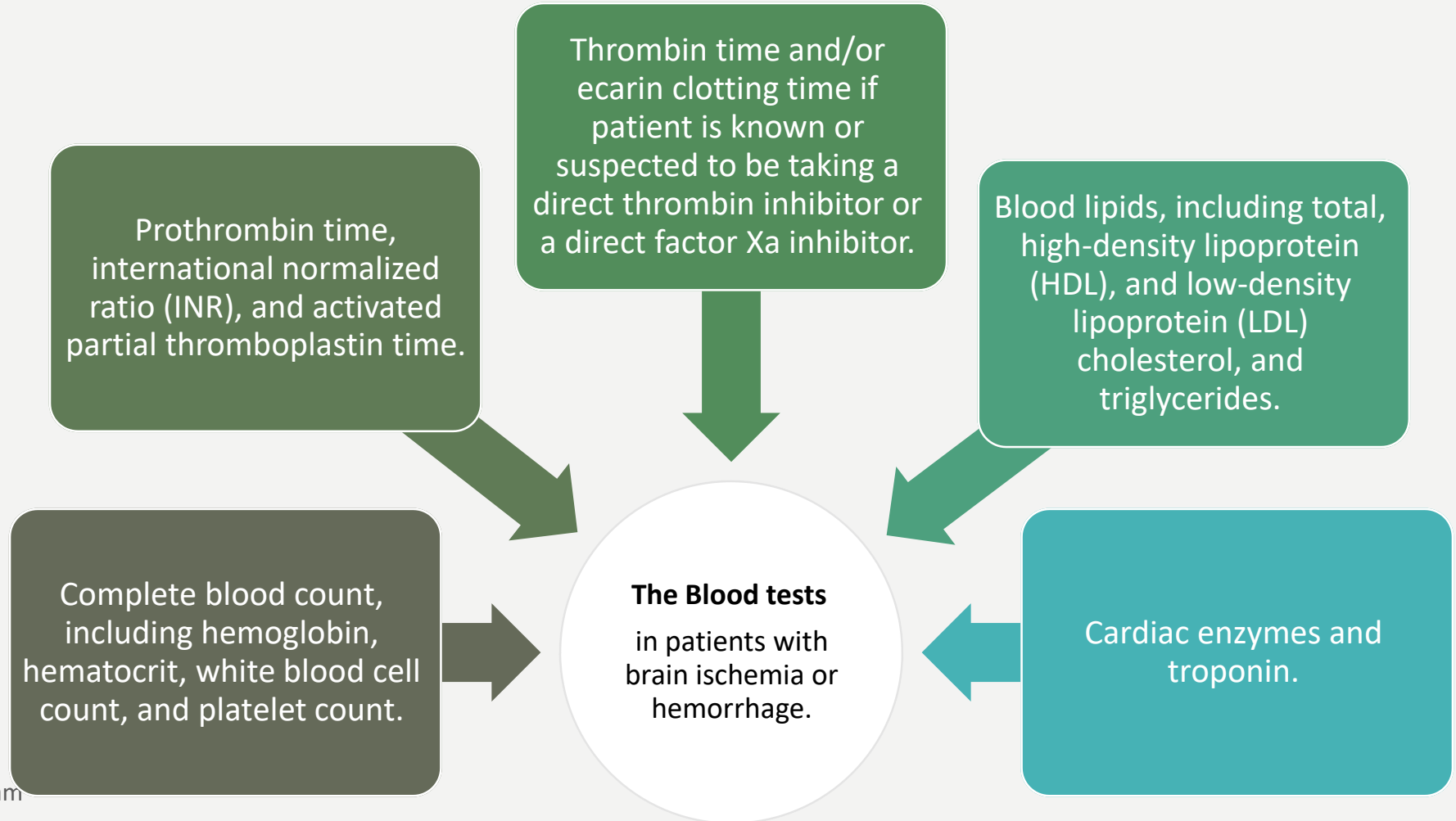
Sources & consequences of increased cytosolic Calcium in cell injury

***Important**



3.Neurochemical Response

- Following cerebral ischemia, extracellular levels of various neurotransmitters are increased e.g., Glutamate, Glycine, GABA, Dopamine.
  *Glutamate and glycine are excitatory: hyper-excited state (neurotoxin)
  *GABA and Dopamine are inhibitory.

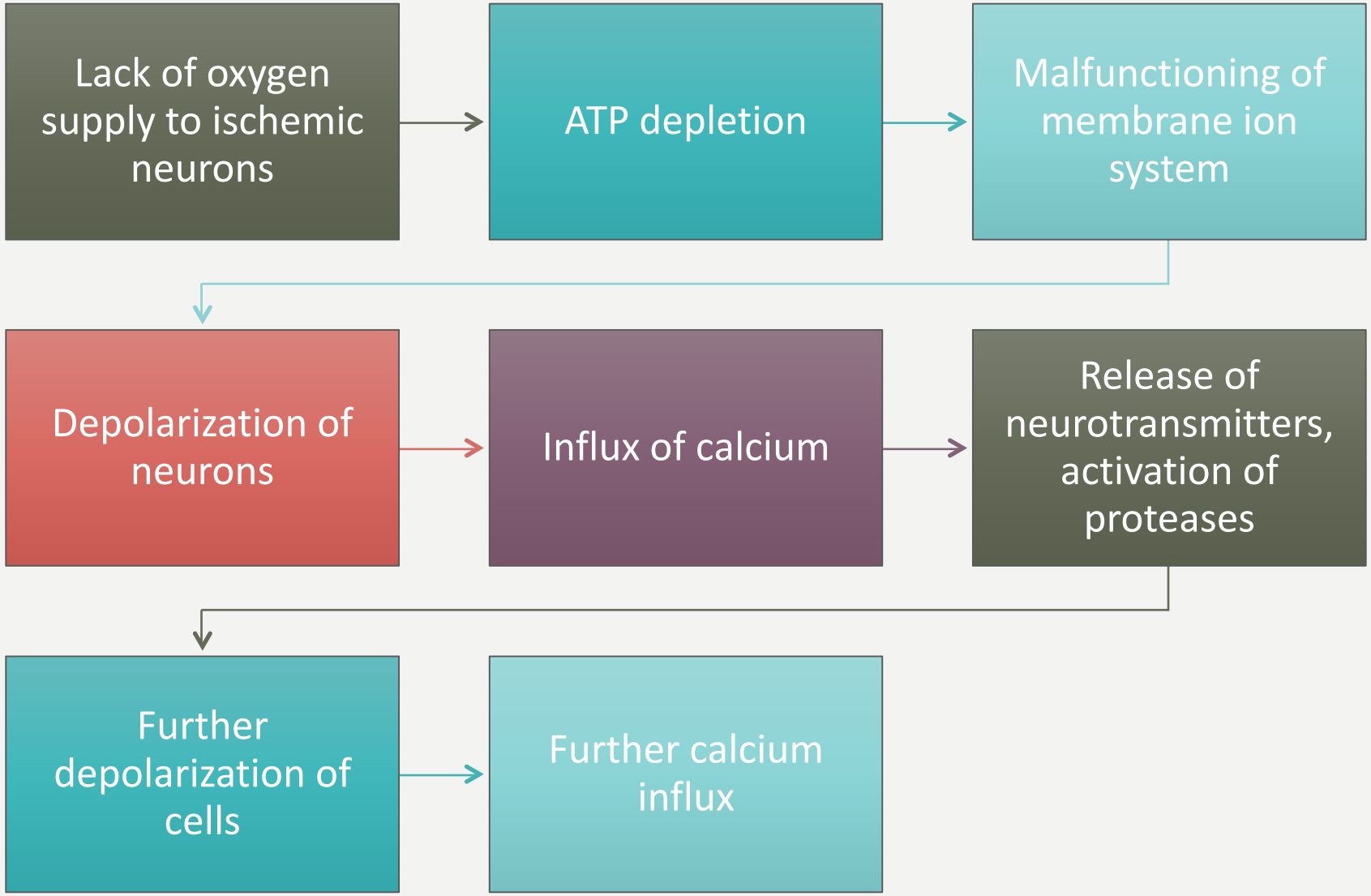


Biochemical Basis Of Pharmacological Intervention

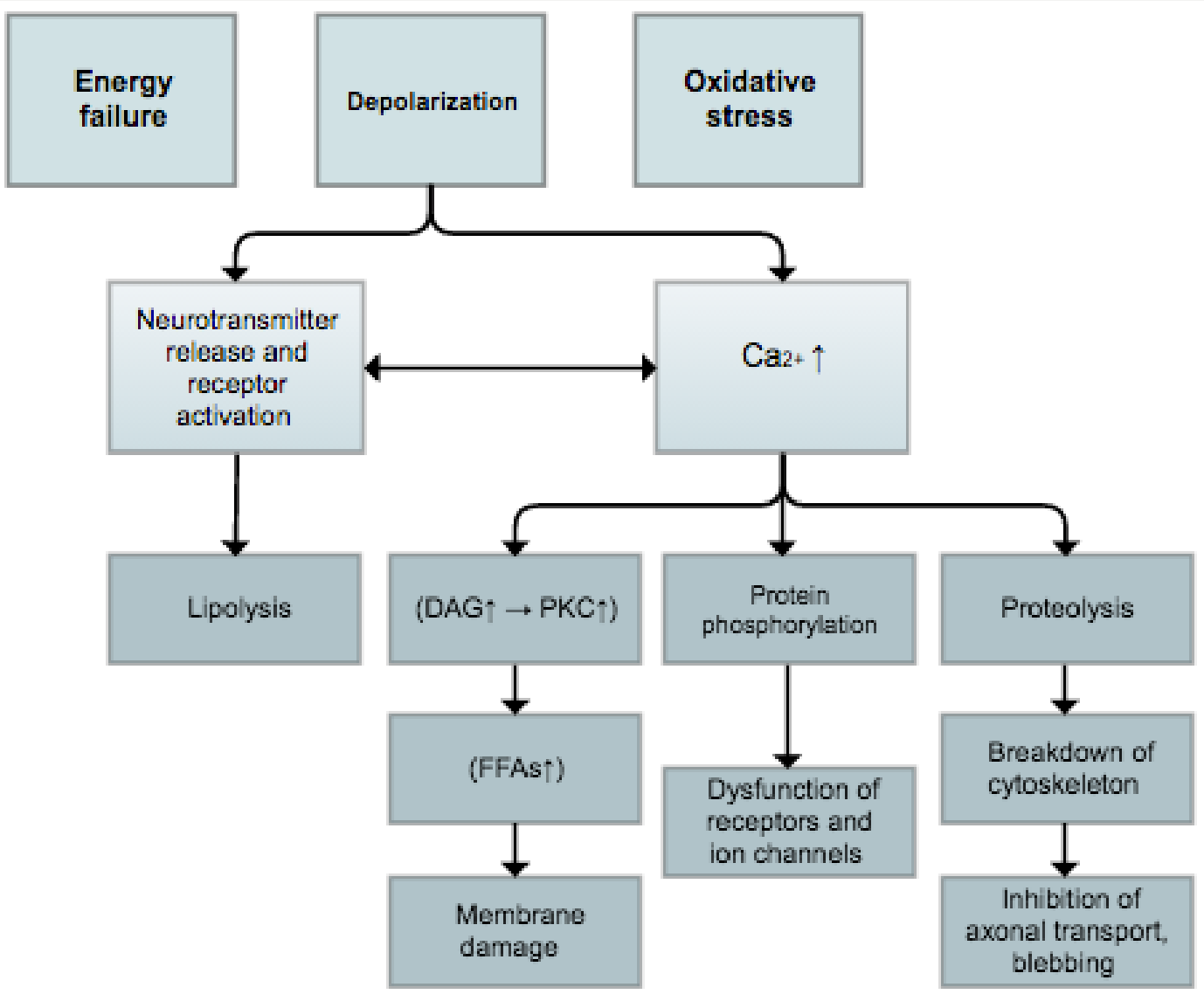
Examples of Potential Biochemical Intervention in Cerebral Ischemia:

- Inhibitors of glutamate release
- Ca2+ channel blockers
- Nitric oxide synthase inhibitors & free radical inhibition
- Calpain inhibitors *because the main damage is done by calpain enzyme.

Summarization of Ischemic Cascade



Consequences of Brain Ischemia



Take Home Message

Severe cerebral ischemic insults lead to a complex cascade of biochemical and molecular events, including:

1. Cell death
2. Oxidative stress
3. Metabolic stress and neurochemical changes

MCQs

1-Which one of the following cell death mechanisms is commonly observed early after severe ischemic insults:

A. Necrosis
B. Apoptosis
C. Toxicosis
D. Phagocytosis

2-Substrates for calpain include:

A. Cytoskeletal protein
B. Membrane protein
C. Regulatory & signaling proteins
D. All of them

3-Oxidative stress is mainly generated by:

A. Astrocytes
B. Oligodendrocytes
C. Microglia
D. A & C

4-Which one of the following is a vascular effect of ROS in ischemic stroke:

A. DNA damage
B. Increased platelet aggregability
C. Protein denaturation
D. Chemotaxis

5-Which one of the following is a beneficial type of NOS:

A. iNOS
B. nNOS
C. eNOS
D. cNOS

1-A
2-D
3-D
4-B
5-C

MCQs

6-Which one of the following induces calpain:

A. Na^+
B. Ca^{++}
C. K^+
D. O_2

7-A condition in which cells are subjected to excessive levels of reactive oxidizing species:

A. Metabolic stress
B. Biochemical response
C. Oxidative stress
D. None of them

8-Oxidative stress has been implicated in which one of the following diseases:

A. Diabetes mellitus
B. Vitamin D deficiency
C. Night blindness
D. Parkinson disease

6-B
7-C
8-D

SAQs

❖ **Q1: Mention 5 reasons that make the brain highly susceptible to ROS-induced damage.**

A: 1- High concentration of perioxidisable lipids. 2- low levels of protective antioxidants. 3- high O2 consumption. 4- high levels of iron. 5- the occurance of reacrions involving dopamine and glutamate oxidase in the brain.

❖ **Q2: Which cell death mechanism occurs after severe ischemic insults & which on occurs after more mild insults ?**

A: Necrosis is commonly observed early after severe ischemic insults while apoptosis occurs with more mild insults.

❖ **Q3: ROS & RNS are generated by ?**

A: They are mainly generated by microglia and astrocytes.

❖ **Q4: Give 4 molecular effects & 2 vascular effects of ROS in ischemic stroke.**

A: Molecular effects: 1- DNA damage. 2- Cytoskeletal damage. 3- protein denaturation. 4- Chemotaxis.

Vascular effects: 1- increased platelets aggregability. 2- increased endothelial cell permiability.

SAQs

❖ **Q5: Mention the benefical & the harmful types of NO & their roles.**

A: Beneficial: NO produced by endothelial NOS (eNOS) → improving vascular dilation and perfusion.

Harmful: NO production by neuronal NOS (nNOS) or by the inducible form of NOS (iNOS) → Increased iNOS activity generally occurs in a delayed fashion after brain ischemia and trauma and is associated with inflammatory processes.

❖ **Q6: what neurotransmitters that are increased following cerebral edema ?**

A: Glutamate, Glycine, GABA & Dopamine

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