Important Doctors slides

Extra Information **Doctors notes**

Biochemistry

Pathogenesis of cerebral infarction

[Editing file]

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

Cerebral Ischemia (Strokes) subtypes:

Stroke

Lack or reduction of blood perfusion in certain area in the brain causing death of the tissue

Hemorrhagic

With 32% global incidence

- Intra-cerebral
- Subarachnoid
  Accumulation in this space the patients describe it as (the worst headache they ever had)

Ischemic

With 68% global incidence

- Thrombotic
- Embolic
  The embolism travels from somewhere else mainly from the heart .

Risk factors of strokes:

- There are a number of risk factors for stroke:

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

The cell death mechanisms implicated in the pathogenesis of **ischemic brain injury**

Hemorrhagic stroke risk factors

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

Ischemic stroke risk factors

1. Age older than 40 years
2. Heart disease
3. High blood pressure
4. Smoking & Diabetes
5. High blood cholesterol levels
6. Illegal drug use
7. Recent childbirth
8. Previous history of transient ischemic attack
   People usually survive from it but if it continue for 24 hours it'll be dangerous.
9. Inactive lifestyle and lack of exercise
10. Obesity
11. Current or past history of blood clots
12. Family history of cardiac disease and/or stroke

Cell death mechanisms in cerebral ischemia : Necrosis and Apoptosis:

- **Necrosis** is commonly observed early after severe ischemic insults
- **Apoptosis** occurs with more mild insults and with longer survival periods
- The mechanism of cell death involves **calcium-induced calpain-mediated proteolysis** of brain tissue

"A condition where the intra-cellular calcium builds up"

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

the cell death can happen by 2 processes: 1- necrosis: it's not programmed cell death and it's abnormal condition .
2- apoptosis: normal and programmed cell death. Both happen after ischemia depending on the duration and the severity of the trauma which one of these two mechanism will happen .

Biochemical Responses to Ischemic Brain Injury :

- ✓ Oxidative stress
- ✓ Metabolic stress
- ✓ Neurochemical response

Oxidative stress

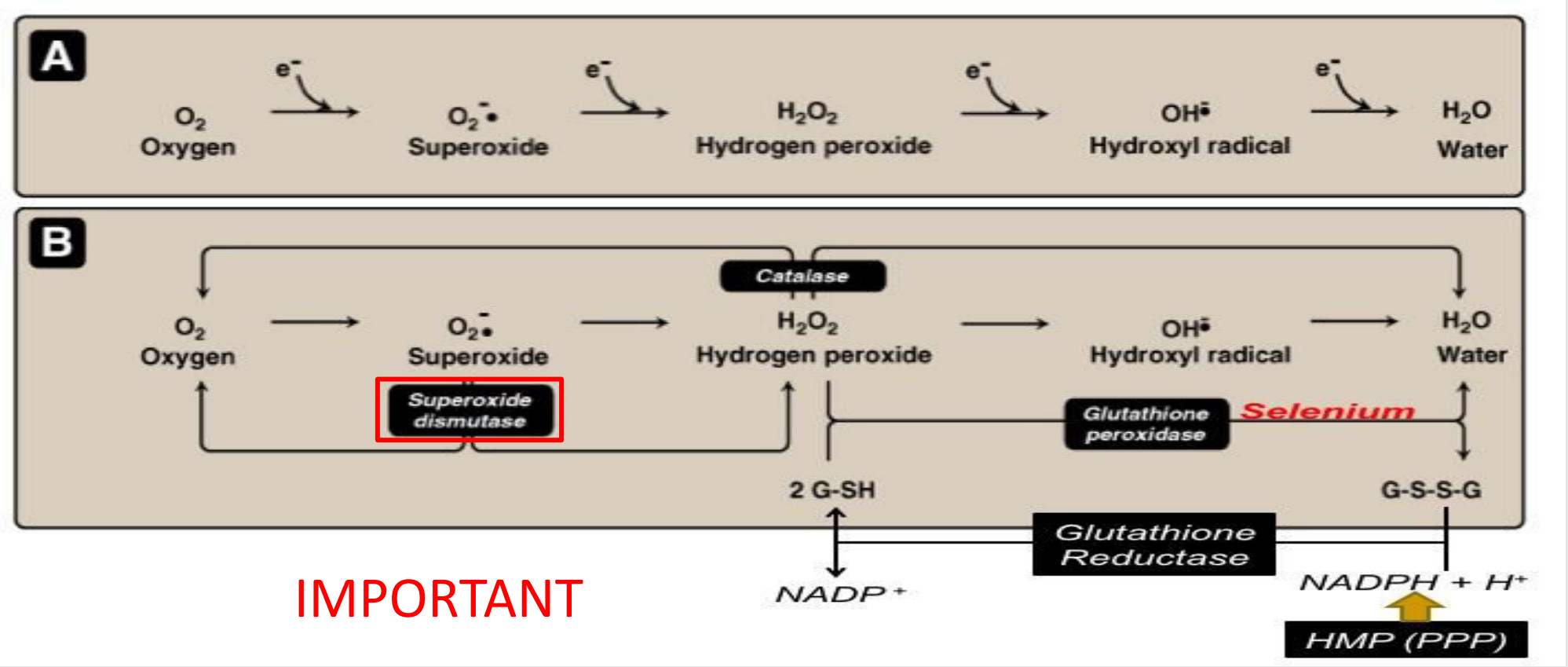
The Role of Reactive Oxygen Species (ROS) & Reactive Nitrate Species (RNS) in Normal Brain Physiology:

- 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 (MBP) by phosphorylation
- They are required for essential processes as learning & memory formation
- They regulate neuronal signaling in both central & peripheral nervous systems
- They are mainly generated by microglia & astrocytes
- They modulate synaptic transmission & non-synaptic communication between neurons & glia

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.

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



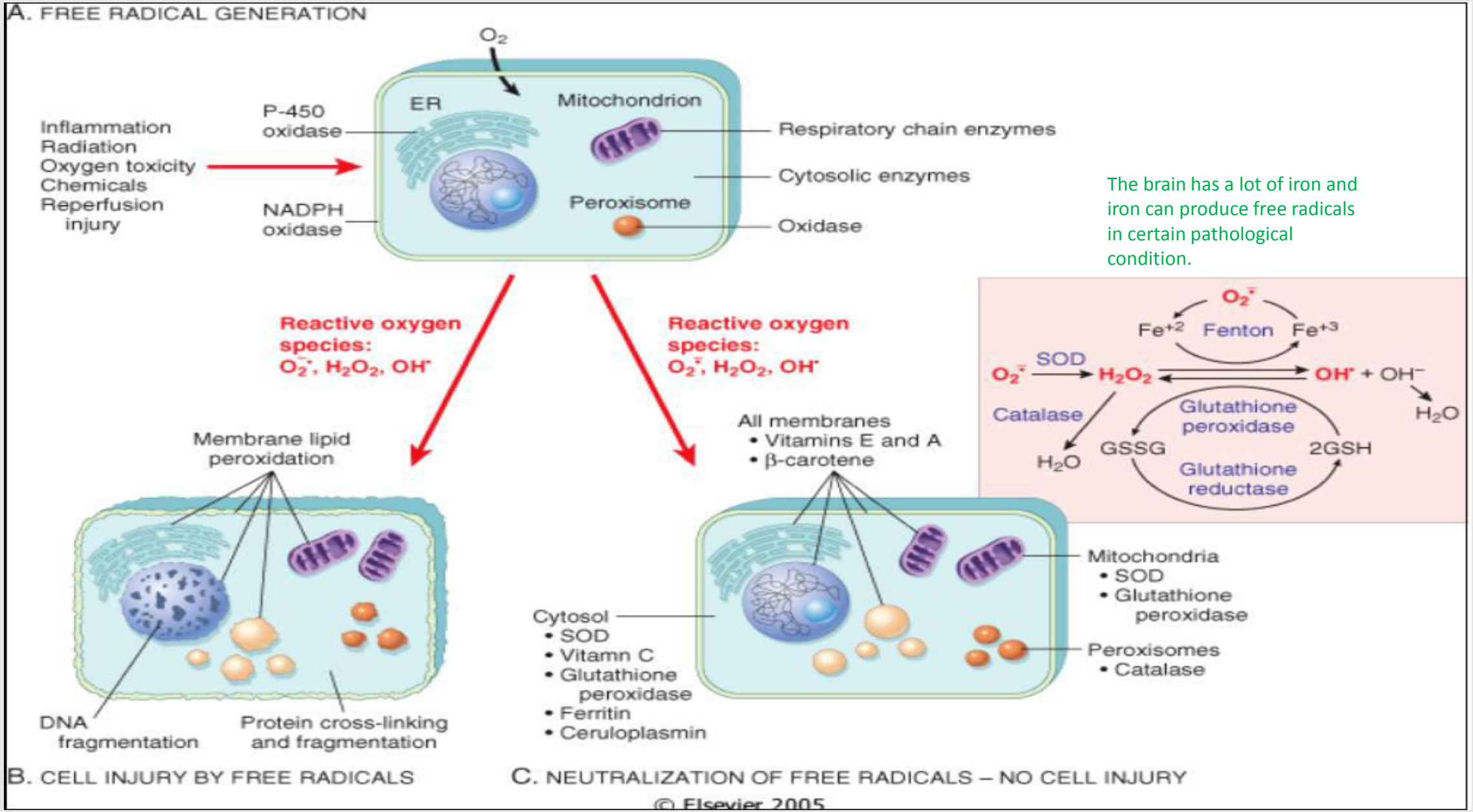
IMPORTANT

When you have less O_2 your mitochondria will not be able to produce enough ATP any type of them also there will be no glucose so, the body will go to anaerobic system but the amount of ATP are so much less and that leads to accumulation of lactate.

A molecule with one free electron called radicals there are very active and they can interact with fat .

There is oxidative stress after ischemia then ROS starts to accumulate .

Generation of free radicals



The brain has a lot of iron and iron can produce free radicals in certain pathological condition.

The brain and Oxidative stress:

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

  - ✓ High concentrations of peroxidisable lipids

    Saturated fatty acids that are normally produce free radicals and the brain has a lot of them.

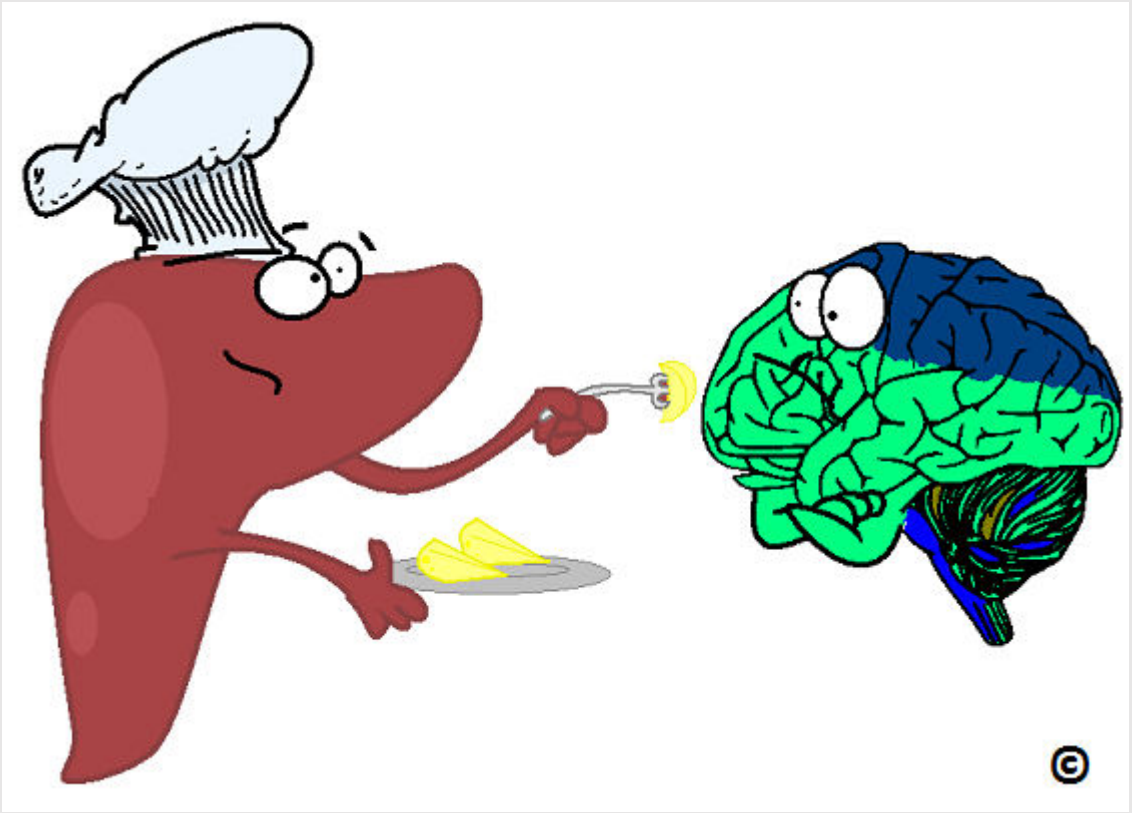
  - ✓ Low levels of protective antioxidants

  - ✓ High oxygen consumption

  - ✓ High levels of iron (acts as pro-oxidants under pathological conditions)

  - ✓ The occurrence of reactions involving dopamine & Glutamate oxidase in the brain

ATP deficiency leads to shut down of NA/K pump because they are ATP dependent also the Ca^{+2}/Na^{+} channels is also shutting down because there is no gradient difference. this lead to accumulation Na and Ca inside the cell, then the water comes in leading swelling of the neuron, then it'll release glutamate which will activate other near neuron, leading extra activation (excitement) of the neurons .



Effects of ROS and NO

Molecular & Vascular effects of ROS in ischemic stroke

1. DNA damage
2. Lipid peroxidation of unsaturated fatty acids
3. Protein denaturation
4. Inactivation of enzymes
5. Cell signaling effects (e.g., release of Ca^{2+} from intracellular stores)
6. Cytoskeletal damage
7. Chemotaxis

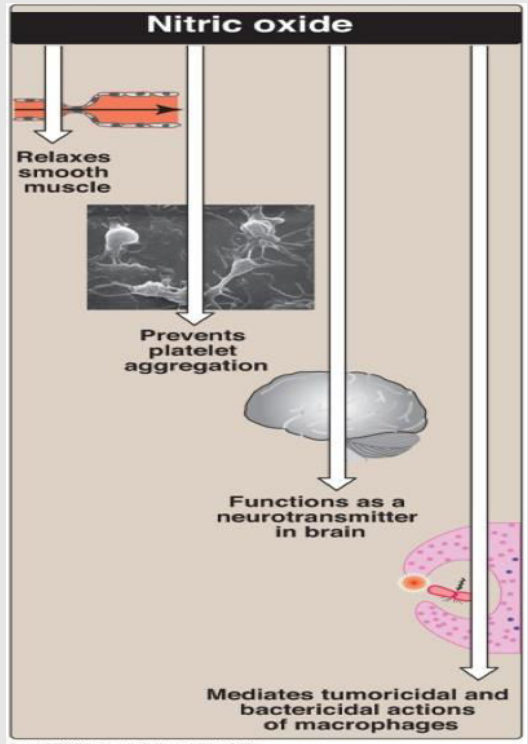
Molecular effects

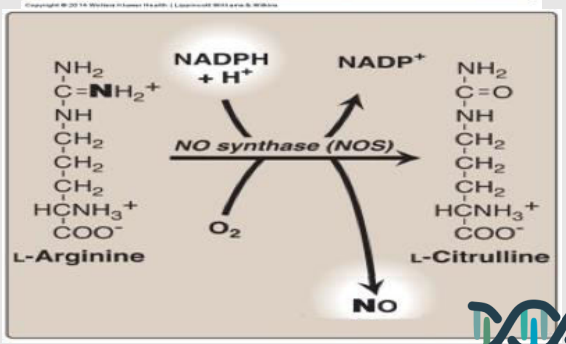
1. Altered vascular tone and cerebral blood flow
2. Increased platelet aggregation
3. Increased endothelial cell permeability

Vascular effects

The role of NO in the pathophysiology of cerebral ischemia

- ✓ Ischemia leads to abnormal production of Nitric oxide and this may be both beneficial and detrimental, depending upon " when and where " NO is released .
- ✓ NO produced by endothelial NOS (eNOS) and causes improvement in vascular dilation and perfusion . In this situation its (beneficial) .
- ✓ In contrast, NO production by neuronal NOS (nNOS) or by the inducible form of NOS (iNOS) has detrimental (harmful) effects .
- ✓ Increased iNOS activity generally occurs in a delayed fashion after brain ischemia and trauma and is associated with inflammatory processes .



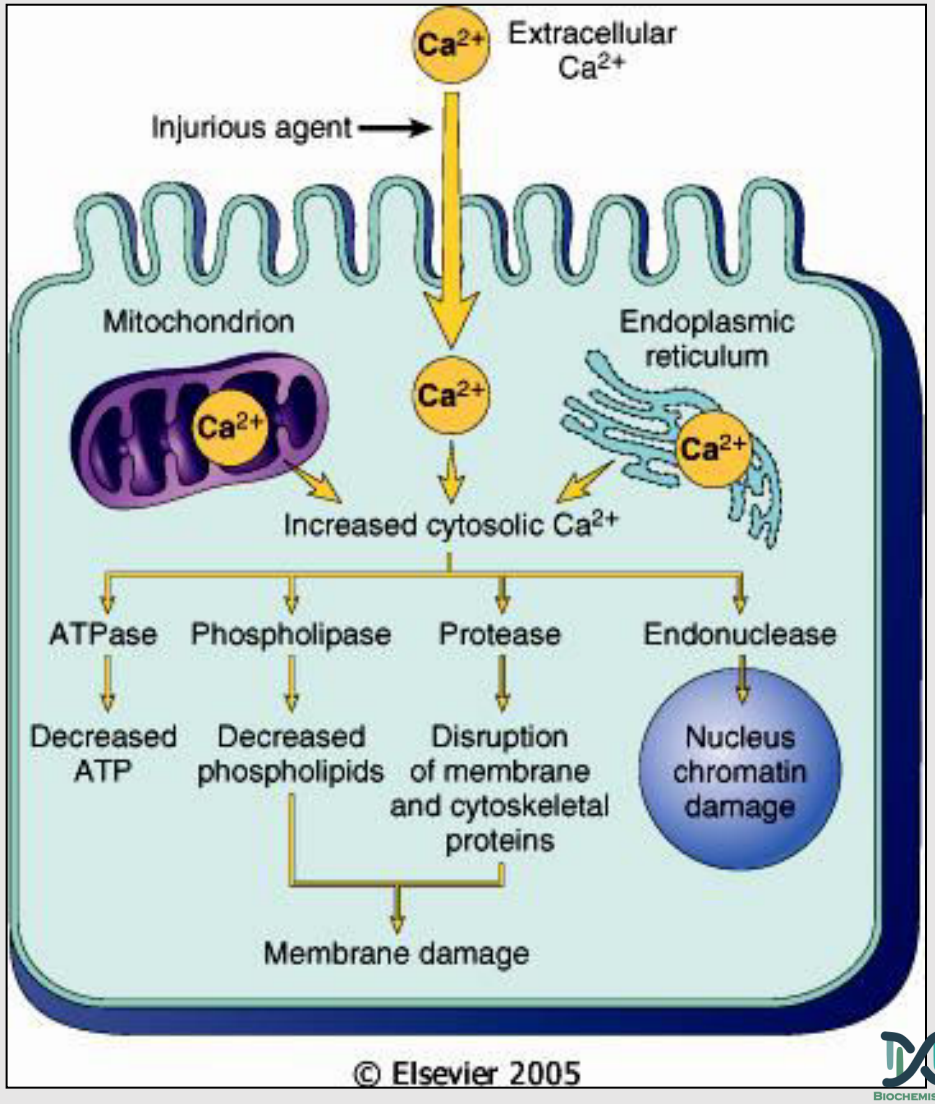


Metabolic stress "The cell starts the anaerobic respiration that lead to acidosis"

Biochemical changes in The brain during ischemia

- Ischemia leads to interruption or severe reduction of blood flow, O2 & nutrients in cerebral arteries → energy depletion (depletion of ATP & creatine phosphate)
- Energy depletion due to inhibition of " ATP dependent ion pumps " which effect membranes depolarization and Perturbance of transmembrane ion gradients .
- Ca^{2+} Influx leads to activation of cellular proteases (Calpains) & lipases which further leads to breakdown of cerebral tissue
- Na^{+} Influx
- K^{+} efflux leading to K+-induced release of excitatory amino acids
- Increased lactic acid in neurons leads to acidosis which promotes the pro-oxidant effect and increases the rate of conversion of O_2^- to H_2O_2 or to hydroxyperoxyl radical

Sources & consequences of increased cytosolic Calcium in cell injury



Neurochemical response

The Blood tests in patients with brain ischemia or hemorrhage

- Complete blood count, including hemoglobin, hematocrit, white blood cell count, and platelet count
- Prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time
- Thrombin time and/or ecarin clotting time if patient is known or suspected to be taking a direct thrombin inhibitor or a direct factor Xa inhibitor
- Blood lipids, including total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, and triglycerides.
- Cardiac enzymes and troponin

Biochemical changes in The brain during ischemia

➢ Following cerebral ischemia, extracellular levels of various neurotransmitters are increased

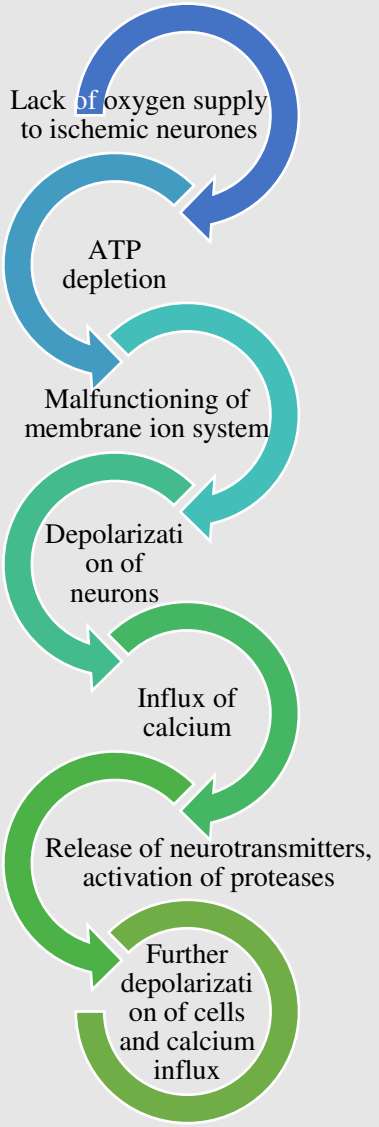
- ✓ Glutamate "Main NT"
- ✓ Glycine
- ✓ GABA
- ✓ Dopamine

Examples of Potential Biochemical Intervention in Cerebral Ischemia

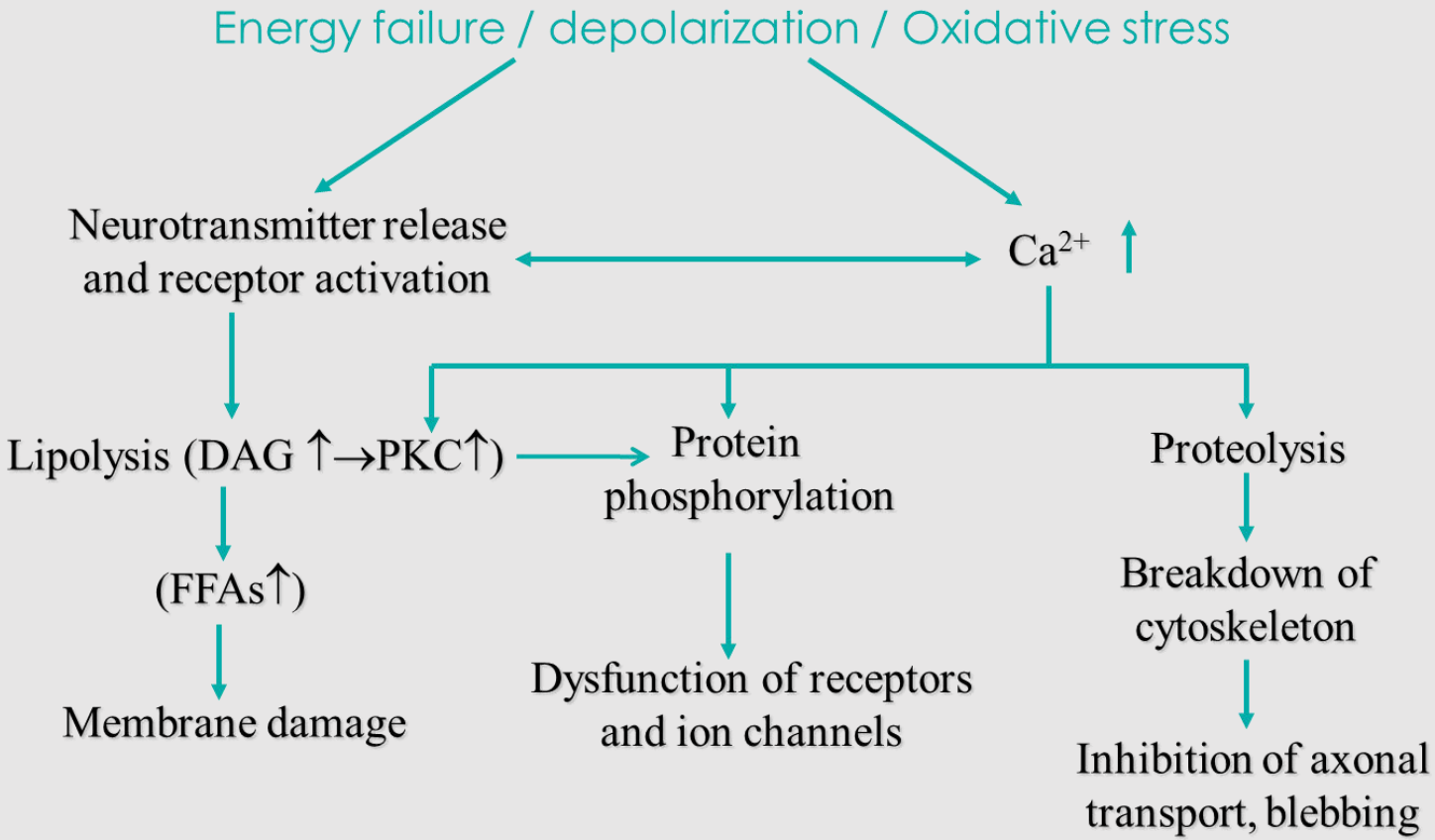
- ✓ Inhibitors of glutamate release.
- ✓ Ca^{2+} channel blockers.
- ✓ Nitric oxide synthase inhibitors & free radical inhibition.
- ✓ Calpain inhibitors

To summarize

Ischemic cascade



Consequences of brain ischemia



Summary

The lecture talked about 3 main aspects:

1- Types of strokes and their risk factors:

Stroke	Hemorrhagic	Ischemic
Types	1- Intracerebral 2- Subarachnoid	1- Thrombotic 2- Embolic
Risk Factors	1. Hypertension 2. Smoking 3. Illegal drug use	
	✓ Blood thinning medications like Warfarin	✓ Has much more risk factors, thus it occurs more commonly than the hemorrhagic type.

2- Cell death in ischemic injury:

Necrosis	Apoptosis
observed early after severe ischemic insults	In more mild insults and with longer survival periods
Involve **calcium-induced calpain-mediated proteolysis** of brain tissue, and **Calpain** includes many proteins; cytoskeletal, membranous, regulatory, and signaling.	

3- The biochemical responses to Ischemic injury:

Oxidative stress	ROS & RNS have important functions in the nervous system. - When cells are exposed to amounts of ROS and RNS, and can't fight them with antioxidants, oxidative stress occurs. - The brain is highly susceptible to ROS damage. - ROS has both molecular and cellular damaging effects. - NO has beneficial vascular effects but harmful neural effects.
Metabolic stress	- Ischemia eventually leads to energy depletion mainly due to inhibition of ATP dependent ion pumps which affects the cell membrane. - Influx: Ca^{2+}, Na^{+} Outflux: K^{+} - Increased lactic acid ➤ acidosis ➤increases conversion of O_2^- to H_2O_2.
Neuro-chemical response	- Extracellular NTs are increased: Glutamate - Glycine - GABA - Dopamine - So as intervention we give inhibitors to Ca^{2+}, Glutamate, NO, free radicals, and calpain.
Required Blood tests	- Complete blood count - Prothrombin time, INR, Activated partial thromboplastin time - Thrombin time, Ecarin clotting time - Blood lipids (HDL, LDL) - Cardiac enzymes and troponin

Quiz

1) Which of the following cell death mechanisms occurs with more mild insults and with longer survival periods ?

a) Necrosis
b) Phagocytosis
c) Apoptosis
d) None of them

2) Which of the following is not a risk factor for ischemic stroke ?

a) Recent child birth
b) Past history of blood clots
c) Warfarin usage
d) Heart disease

3) The enzyme that converts superoxide to hydrogen peroxide is ?

a) NADPH oxidase
b) Superoxide dismutase
c) Catalase
d) Glutathione peroxidase

4) Which of the following is not an effect of ROS in an ischemic stroke ?

a) DNA damage
b) Decrease platelet aggregability
c) Increased endothelial permeability
d) Inactivation of enzymes

5) ROS & RNS are mainly generated by ?

a) Microglia and astrocytes
b) Oligodendrocytes
c) Schwann cells
d) Myelin sheath

Q : How can NO have beneficial and harmful effect ?

Q : Describe the ischemic cascade ?

Q: What are the vascular effects of ROS ?

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

Suggestions and recommendations

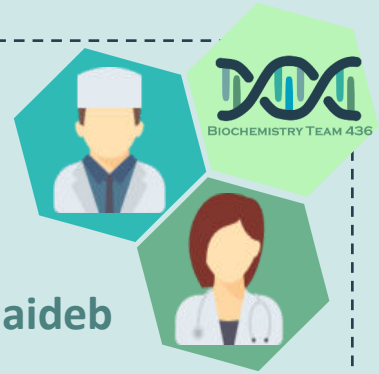
Biochemistry Team 436

TEAM LEADERS

Mohammad Almutlaq

Rania Alessa

TEAM MEMBERS



Qaiss almuhaideb

Haifa bin taleb

Shatha Algehib

Nourah Alshabib

Ameerah Nyazi

THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

- Lippincott's Illusrated Reviews Biochemistry 6th E

https://www.youtube.com/watch?v=lnYqZZgqxNs

Don’t forget to review the notes

@436Biochemteam

Biochemistryteam436@gmail.com