Biochemistry
Team 434

Pathogenesis of cerebral ischemia

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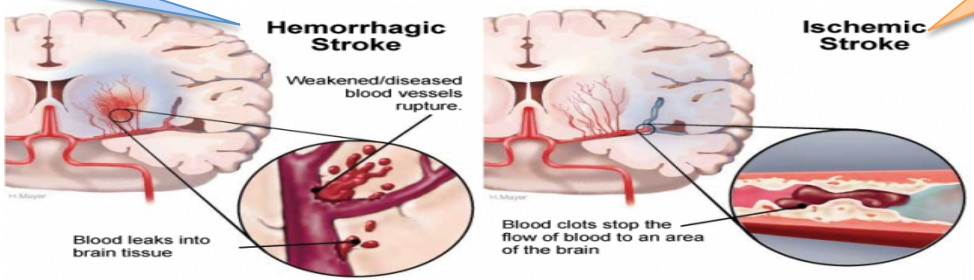
Subtypes of Cerebral Infarction (Stroke)

- **Hemorrhagic**
  - Intracerebral
  - Subarachnoid
- **Ischemic**
  - Thrombotic
  - Embolic

Global incidence: 32%

Global incidence: 68%



Characteristics of stroke subtypes

Stroke type	Clinical course	Risk factors	Other clues
1.Intracerebral hemorrhage	**Gradual** progression (min –hrs)	• **HTN*** • Trauma • Bleeding diatheses • Vascular malformations • Certain races • Ilicit drugs	May be precipitated by physical activity. Patient may have reduced alertness.
2.Subarachnoid hemorrhage	**Abrupt** onset of sudden, severe headache.	• Smoking • **HTN*** • Alcohol • sympathomimetic drugs • Genetic susceptibility (family history of subarachnoid hemorrhage) *Hypertension	
3.Ischemic (thrombotic)	Stuttering progression with periods of improvement. Lacunes develop **over hours or at most a few days;** large artery ischemia may evolve over longer periods.	Atherosclerotic risk factors (age, smoking, DM, etc.). Men affected more commonly than women. May have history of **TIA****. **transient ischemic attack.	May have neck bruit.
4.Ischemic (embolic)	**Sudden onset** with deficit maximal at onset. Clinical findings may improve quickly.	Atherosclerotic risk factors. Men affected more commonly than women. History of **heart disease**	Can be precipitated by getting up at night to urinate, or sudden coughing or sneezing.

Globally:

- Stroke is the 2nd most common cause of **mortality**
- Stroke is the 3rd most common cause of **disability**

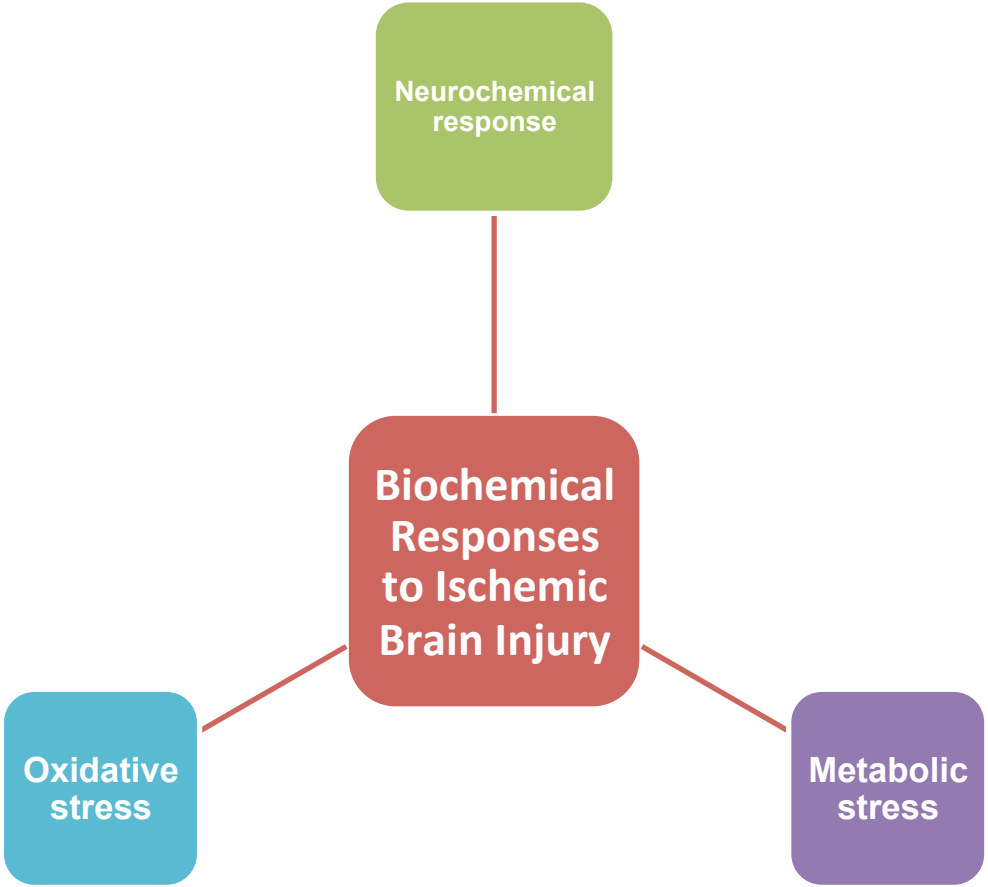
Stroke			
	High-income countries	**Low-income countries**	
Incidence	↓	↑	• Men > women(at younger but not older ages) • Women> Men (≥75 year old)
Mortality	↓	↓	
The absolute number of people with stroke, stroke survivors, stroke-related deaths, and the global burden of stroke-related disability is: **high and increasing**			

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

Substrates for calpain include:

- Cytoskeletal proteins
- Membrane proteins
- Regulatory and signaling proteins

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


Neurochemical response
Biochemical Responses to Ischemic Brain Injury
Oxidative stress
Metabolic stress

Oxidative stress

Oxidative stress

Defintion..?

- ➢ A condition in which cells are subjected to:
- ✓ excessive levels of Reactive oxidizing species (Oxygen or nitrative species),
- ✓ they are unable to counterbalance their deleterious effects with antioxidants.

Implicated in..?

the ageing process & in many diseases

(e.g., atherosclerosis, cancer, neurodegenerative diseases, stroke)

They regulate neuronal **signaling** in both CNS & PNS.

They are required for essential processes as **learning & memory** formation

The Role of (ROS+RNS)in Normal Brain Physiology..?

mainly generated by microglia & astrocytes

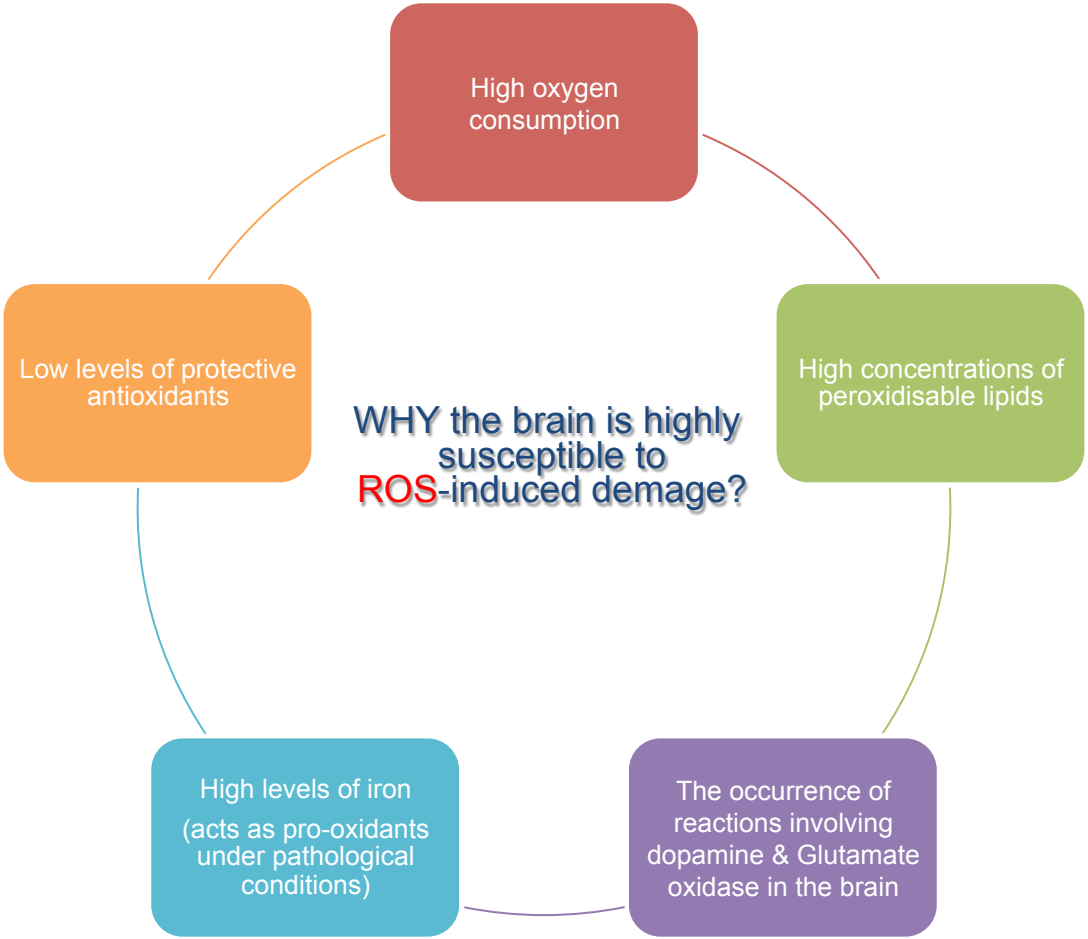
They modulate synaptic transmission & non-synaptic **communication** between neurons & glia

During periods of increased neuronal activity, ROS & RNS diffuse to the myelin sheath of oligodendrocytes activating

Protein kinase C (**PKC**) → post translational modification of myelin basic protein (**MBP**) by phosphorylation

The brain and Oxidative stress

Oxidative stress



Molecular & Vascular effects of ROS in ischemic stroke

Oxidative stress

Molecular effects:

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

Vascular effects

- Altered vascular tone and cerebral blood flow
- **Increased** platelet aggregability
- **Increased** endothelial cell permeability (Edema)

Oxidative stress

The role of NO in the pathophysiology of cerebral ischemia

Ischemia→ abnormal NO production
This may be both beneficial and detrimental, depending upon when and where NO is released

Endothelial NOS (eNOS) → improving vascular dilation and perfusion	Neuronal NOS (nNOS)	Inducible NOS (iNOS) -Generally occurs in a delayed fashion after brain ischemia and trauma and is associated with inflammatory processes.
(i.e. beneficial).		has detrimental (harmful) effects.

Metabolic stress

Biochemical Changes in the Brain During Ischemia

Ischemia will lead to the decrease of: **blood flow, oxygen and nutrients in the cerebral arteries.**

This will in turn cause energy depletion, where there will be a deficit of ATP and creatine phosphate. This will result in one of two situations:

Inhibition of ATP-dependant ion pumps that are responsible for membrane depolarization;
- Ca2+ influx (translocation from extracellular to intracellular spaces)

Activation of cellular proteases (calpains) and lipases.

Breakdown of cerebral tissue
– Na+ influx
-K+ efflux (K+ induces the release of excitatory amino acids)

Increase in lactic acid in neurons as they turn to anaerobic glycolysis.

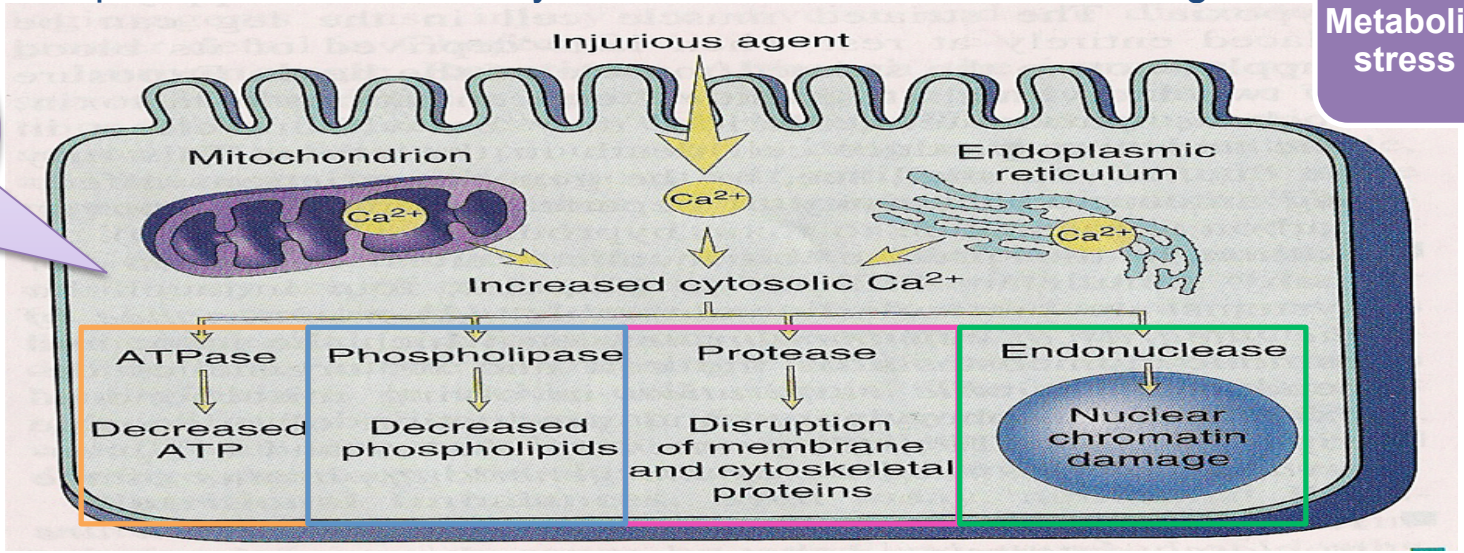
This will cause acidosis and therefore promote a pro-oxidant effect

that will increase the rate of oxygen conversion into free radicals.

Metabolic stress

Consequences of Increased Cytosolic/Intracellular Calcium During Cell

Calcium influx detrimental effects, including:



Neurochemical response

Neurochemical Response to Ischemia

extracellular levels of various neurotransmitters are increased, such as:

- Glutamate
- Glycine
- GABA
- Dopamine

Blood Tests in Patients With Brain Ischemia or Hemorrhage

Tests include:

- CBC (hemoglobin, hematocrit, white blood cell count and platelet count)
- Prothrombin time, international normalized ratio (INR) and activated partial thromboplatin time
- Thrombin time and/or ecarin clotthing time (recommended if patient is known or suspected to be taking a direct thrombin inhibitor or a direct factor Xa inhibitor)
- Blood lipis, including total, high density lipoprotien (HDL), low density lipoprotien (LDL), cholestrol and triglycerides
- Cardiac enzymes and troponin

Potential Biochemical Intervention in Cerebral Ischemia

Examples include:

- Inhibitors of glutamate release
- Ca2+ channel blockers
- Nitric oxide synthase inhibitors and free radical inhibition
- Calpain inhibitors

MCQs

1-which one of the following cell death mechanisms happen after severe ischemic insults?

a-necrosis b-apoptosis c-dystrophic calcification

2-oxidative stress has implicated in which one of the following diseases?

a-parkinson b-multiple sclerosis c-night blindness

3-ROS and RNS are mainly generated by microglia and astrocyte?

a-true b-false

4-which one of the following is a substance for calpain?

a-cytoskeletal proteins b-membrane proteins c-regulatory and signaling proteins d-all of them

5-a condition in which cells are subjected to excessive levels of reactive oxidizing species?

a-oxidation stress b- metabolic stress c-biochemical response d-none of them

6-NO production by nNOS and iNOS has a beneficial effects?

a-true b-false

answers:1-a 2-a 3-a 4-d 5-a 6-b

SAQs

Q1- list 4 molecular effects of ROS in ischemic stroke?

1-dna damage 2-proteins denaturation 3-inactivation of enzymes 4-chemotaxis

Q2-the brain is highly susceptible to ROS induced damage,why?

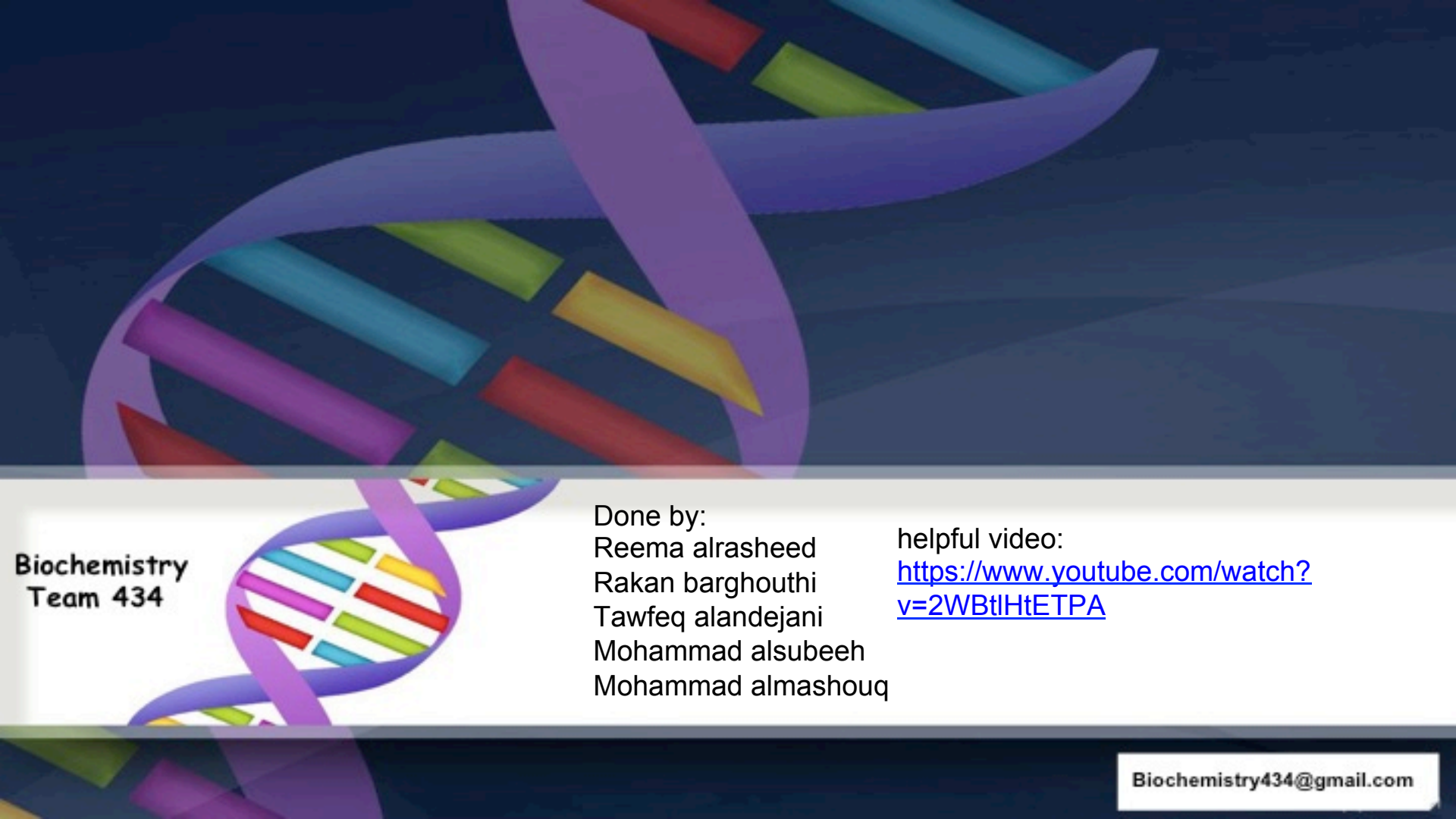
1-high conc of peroxidizable lipids 2-low levels of protective antioxidants
3-high O2 consumption 4-high levels of iron

Q3-explain the role of ROS and NOS in normal physiology of the brain?

1-they modulate the synaptic transmission and non synaptic communication between neurons and glia 2-they regulate neuronal signaling in both cns and pns
3-they are required for essential processes as learning and memory formation

Q4-list 3 various neurotransmitters that their extracellular levels will increase following cerebral ischemia?

1-glutamate 2-GABA 3- dopamine



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helpful video:
https://www.youtube.com/watch?v=2WBtlHtETPA

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