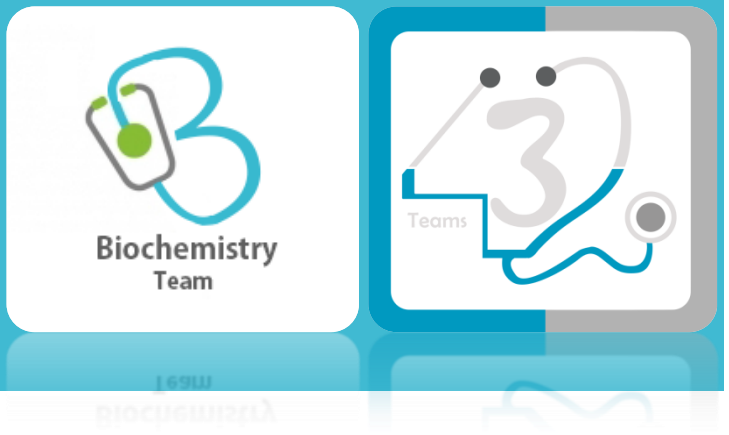
[lecture 3]

Pathogenesis of Cerebral Infarction at Cellular & Molecular Levels



The Objectives

- **Objectives:**

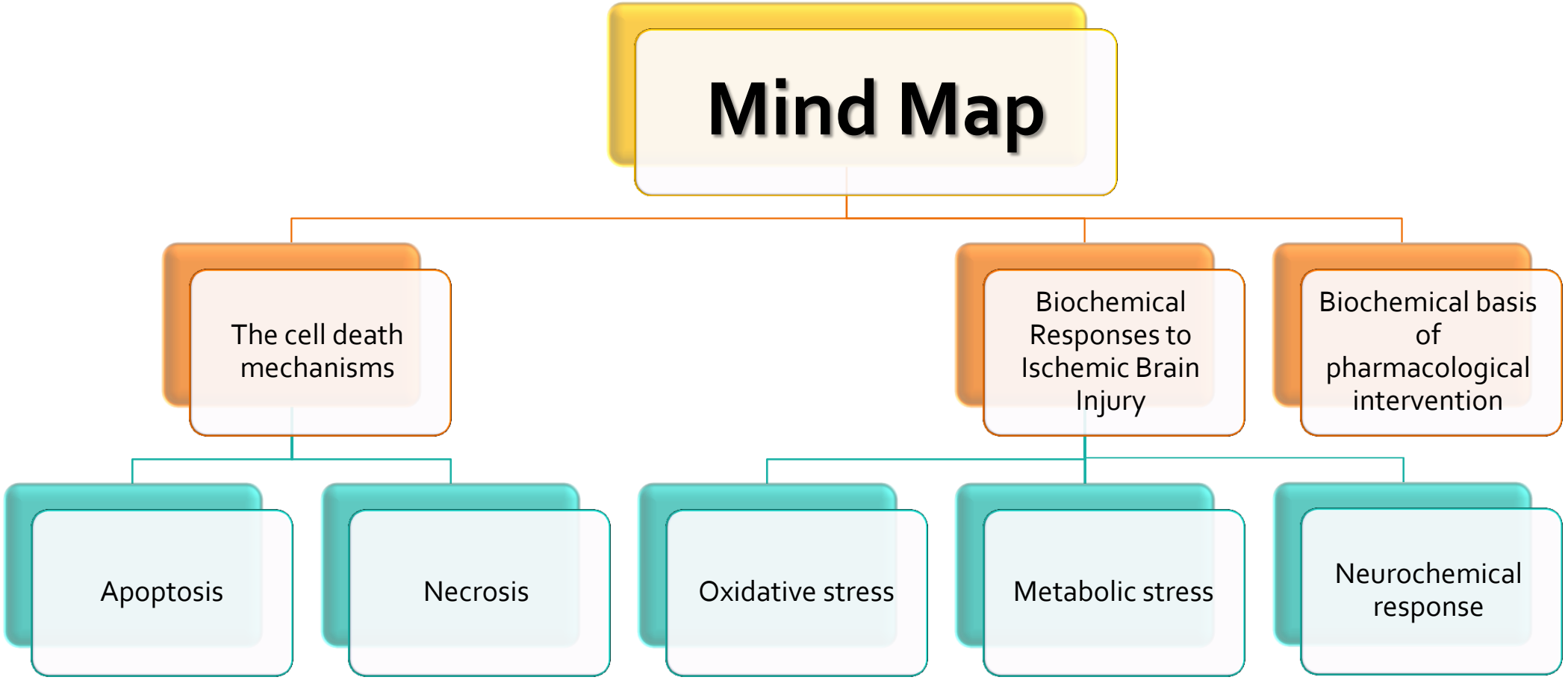
- ❑ Identify the possible **cell death mechanisms implicated in the pathogenesis of ischemic brain injury**
- ❑ Acquire the knowledge of the important role played by **oxidative stress and free radicals in the pathogenesis of cerebral infarction**
- ❑ Understand the various factors involved in **ischemia-induced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

Red = Import-ant

Blue = explain

Green = addition notes

Done By : Asma Al-Mohizae - Ameera Al-Amri - Lama Al-Fraidi


Mind Map
The cell death mechanisms
Biochemical Responses to Ischemic Brain Injury
Biochemical basis of pharmacological intervention
Apoptosis
Necrosis
Oxidative stress
Metabolic stress
Neurochemical response

The cell death mechanisms

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

Necrosis: is commonly observed early after severe ischemic insults

Apoptosis: occurs with more mild insults and with longer survival periods

It may happen both depend on the severity and time

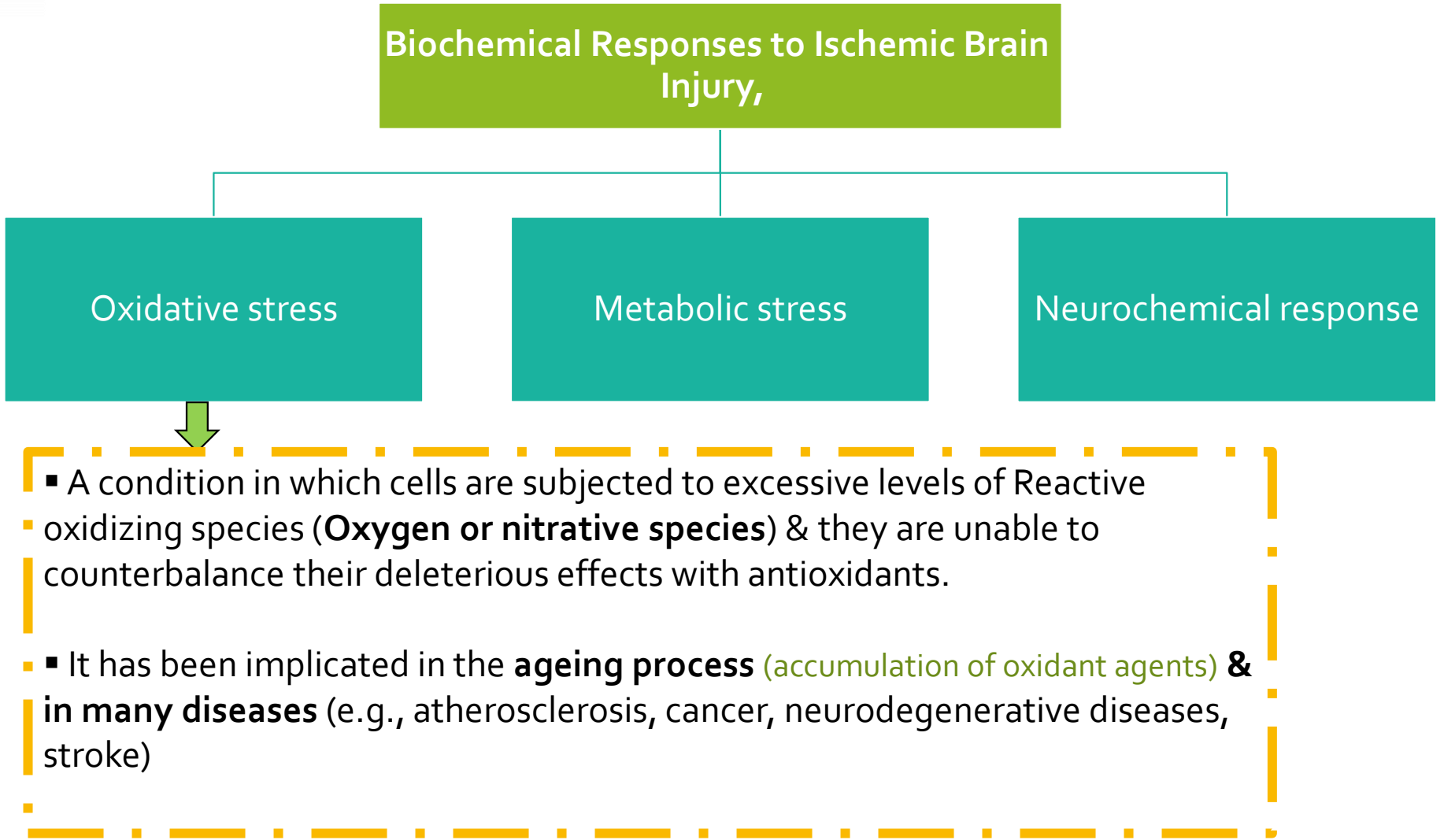
The mechanism of cell death involves calcium-induced **calpain-mediated proteolysis of brain tissue** (enzymes that degrades the membrane proteins)

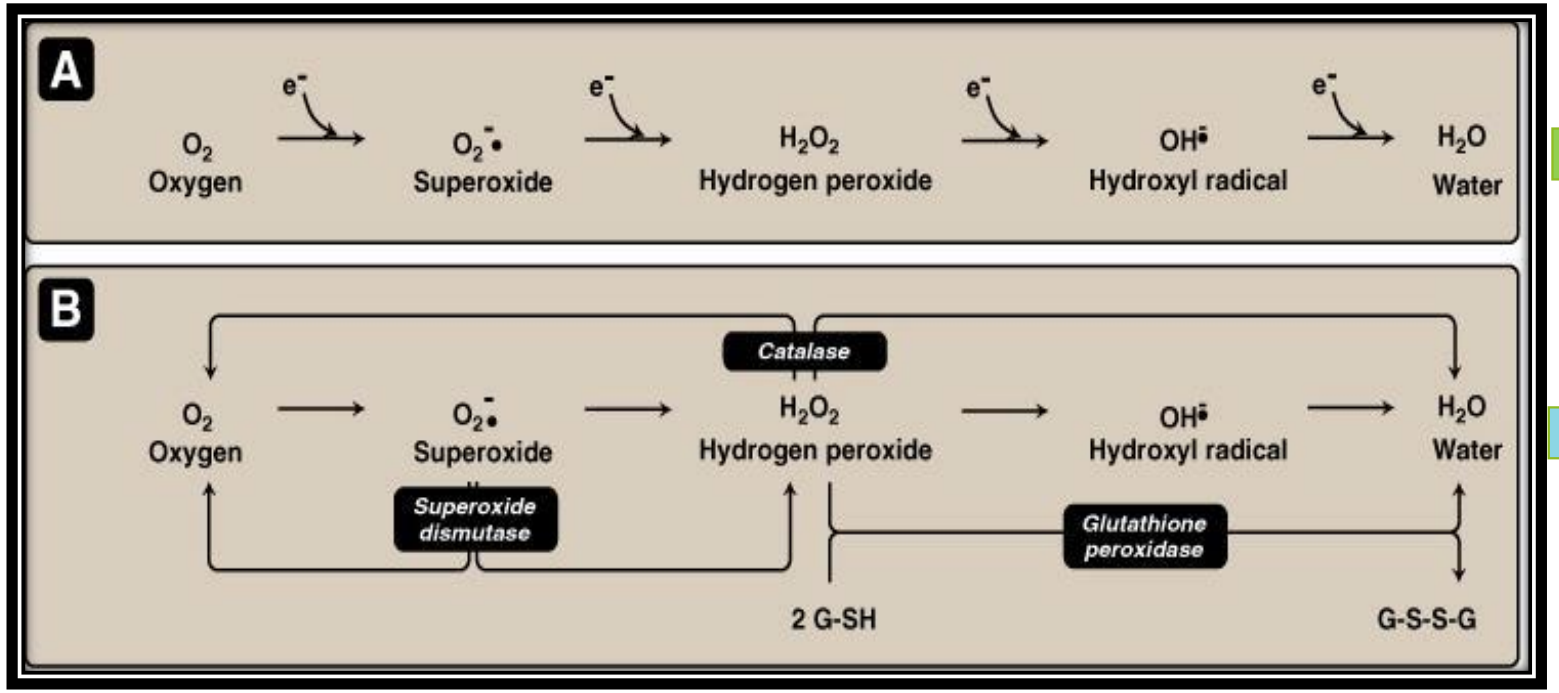
The role of calcium is important in cerebral ischemia (increase in intracellular ca) → activating calpain-mediated proteolysis → degrades the protein in the brain

Substrates for calpain include: (calpain is calcium dependent)

- **Cytoskeletal proteins**
- **Membrane proteins**
- **Regulatory and signaling proteins**

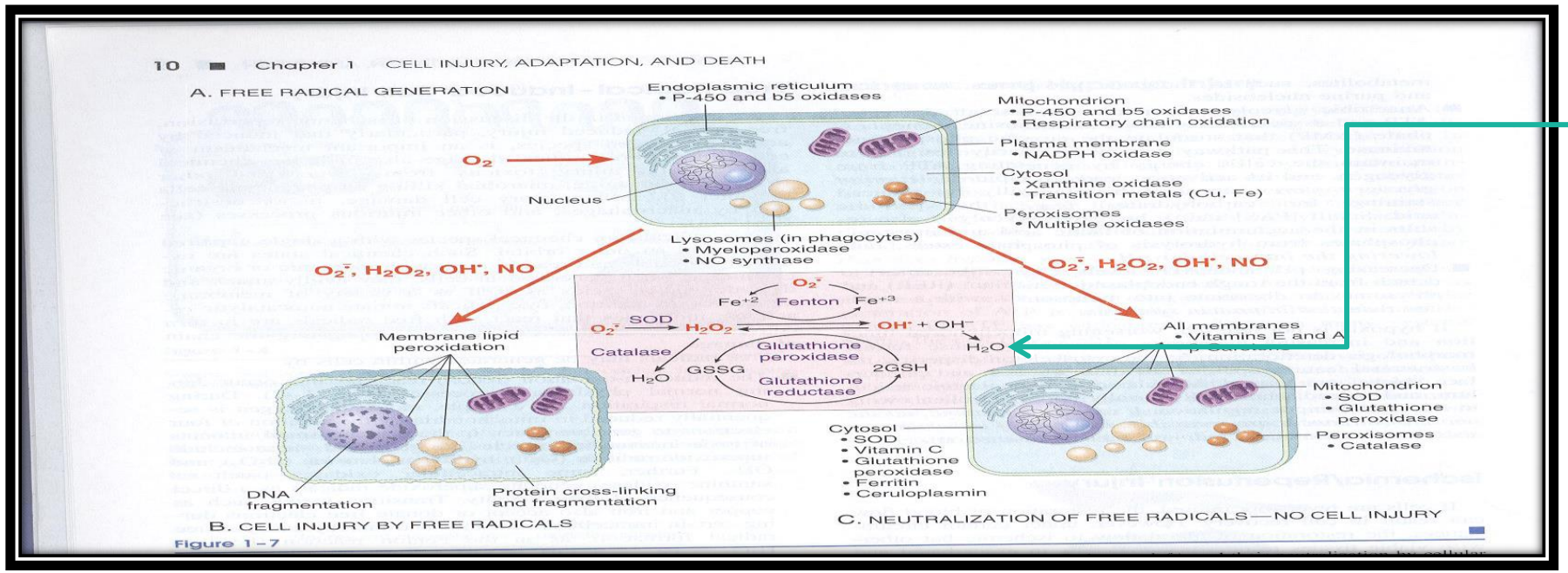
Biochemical Responses to Ischemic Brain Injury





Reduction of oxygen to water that occur in mitochondria (ETC), During this conversion very reactive species form (ROS).

Enzymes (antioxigants) inside the cell, that help to prevent ROS to go outside the mitochondria.



Fenton reaction: the role of conversion from ferric (Fe^{3+})to **Ferrous** (Fe^{2+}), that form ROS **especially superoxide ion and hydroxyl radical.**

There are agents other than enzymes protect the cell against excess oxidative stress e.g. (vit C, vit A and the precursor of vit A (carotenoids))

(A) 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) (add phosphate on protein) (calcium dependent) → posttranslational modification of myelin basic protein (MBP) by phosphorylation

This is normal physiology

- They regulate neuronal signaling in both central & peripheral nervous systems

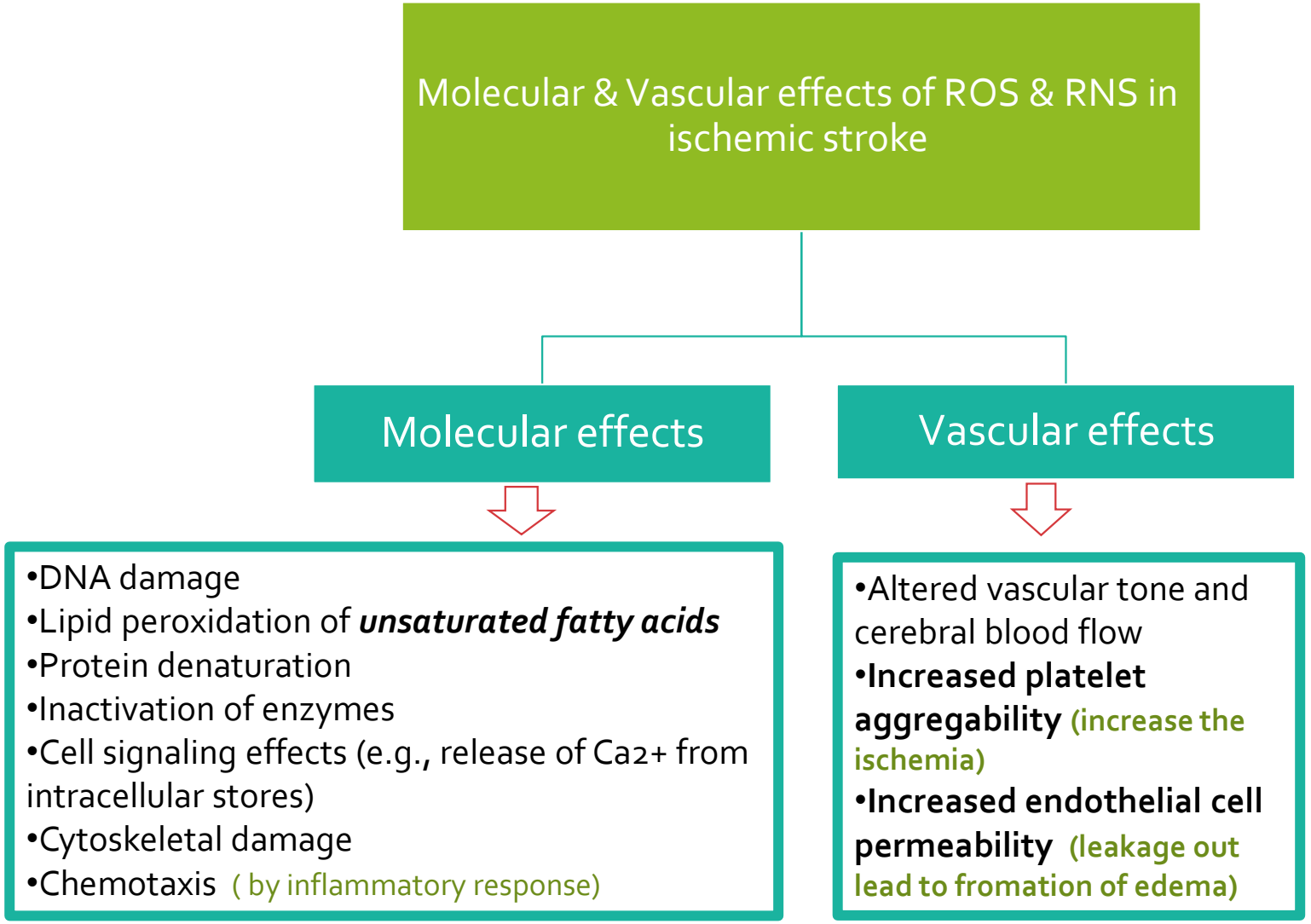
- They are required for essential processes as **learning & memory formation**

Cont, Oxidative stress

The brain and Oxidative stress

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

- ❑High concentrations of **peroxidisable lipids (especially unsaturated fatty acids)**
- ❑Low levels of protective antioxidants
- ❑High oxygen consumption
- ❑High levels of iron (**acts as pro-oxidants under pathological conditions)** (copper may acts as pro-oxidant)
- ❑The occurrence of reactions involving dopamine & Glutamate oxidase in the brain



The role of NO in the pathophysiology of cerebral ischemia

Biochemistry Team

Ischemia → Abnormal NO production

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

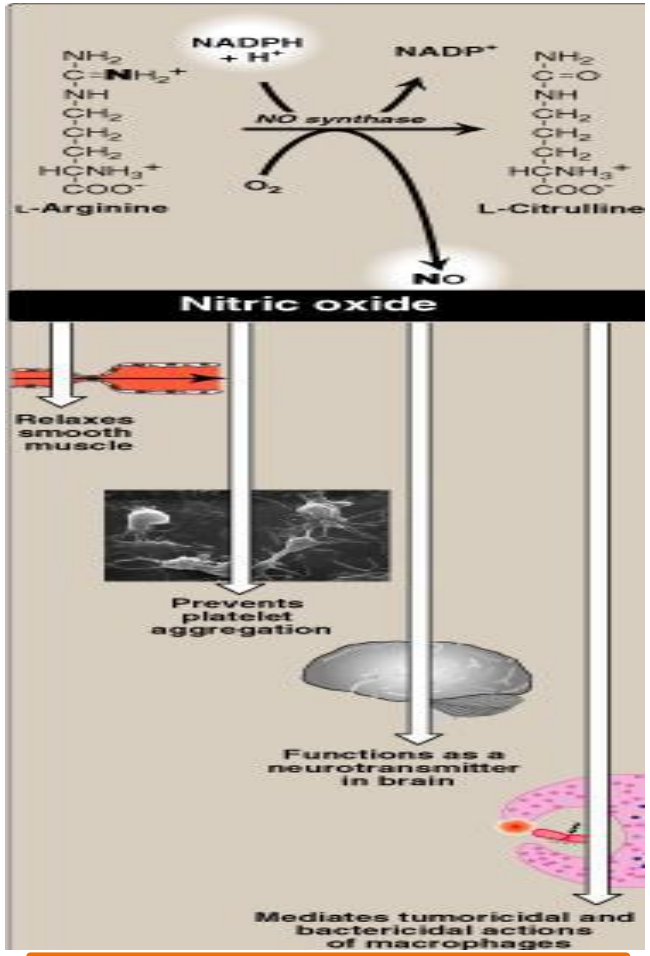
Beneficial →

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

Detrimental →

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



NO produced by No synthase

The picture show you beneficial of NO

(B)Metabolic stress

- Many biochemical changes happen when the brain undergoes ischemia. One such event is the metabolic stress. The ischemic cascade by which this happens is as follows:

(1) Ischemia (hypoperfusion) → (2) Severe reduction of (O_2 + nutrients) in the cerebral arteries

(3) Energy depletion. ATP and creatine phosphate (energy currency)

Inhibition of ATP-dependent ion pumps which results in:	Depletion of O_2 ➔ cell resorts to inaereobic metabolism

• Membrane depolarization
• Perturbance of transmembrane ion gradients (mainly Ca^{+2})
  • Ca^{+2} influx: translocates from ECF to ICF ➔ Activation of Ca^{+2} dependent proteases (calpains) and lipases ➔ Breakdown of cerebral tissue.
  • Na^{+} influx
  • K^{+} efflux ➔ K^{+} induced release of excitatory amino acids
	• Increased lactic acid in the neurons:
	  • Acidosis
	  • Besides the deleterious effect of ↓ pH , it promotes the pro-oxidant effect ➔ increases conversion of O_2^{-} to H_2O_2 or to hydroxyperoxyl radical.

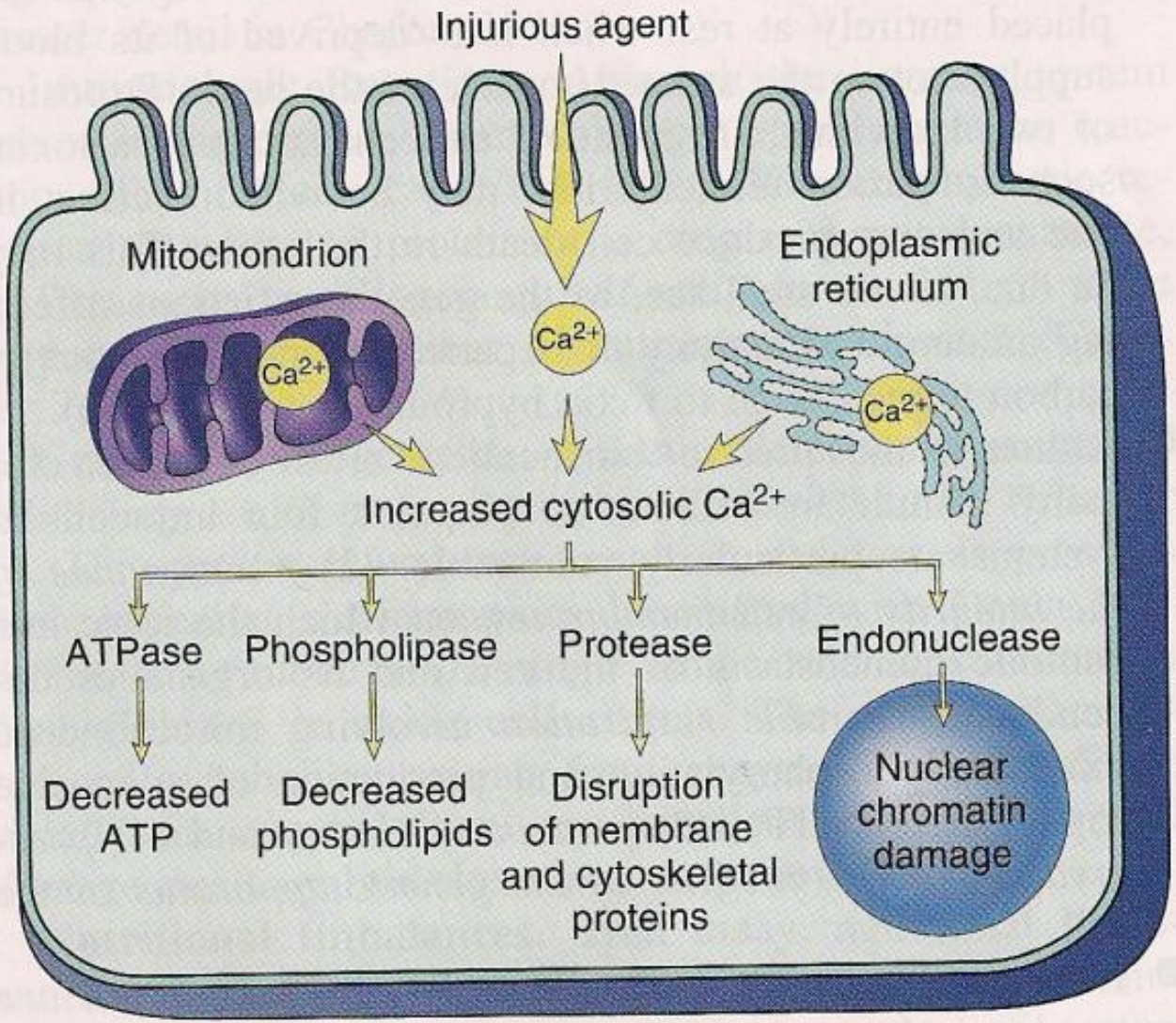
Sources and consequences of increased cytosolic calcium in cell injury

- The picture demonstrates that the increased intracellular calcium does not only result from calcium influx but also from sources intrinsic to the cell such as sites of storage. The increased levels of Ca^{+2} then cause injury through release of enzymes that are detrimental to the cell such as energy depletion.

(C) Neurochemical response

Following cerebral ischemia, extracellular levels of various neurotransmitters increase; such as:

1)Glutamate
2)Glycine
3)GABA
4)Dopamine



Biochemical basis of pharmacologic intervention

- We must first know the mechanism by which injury happens to find our targets in therapy.

Inhibitors of glutamate release

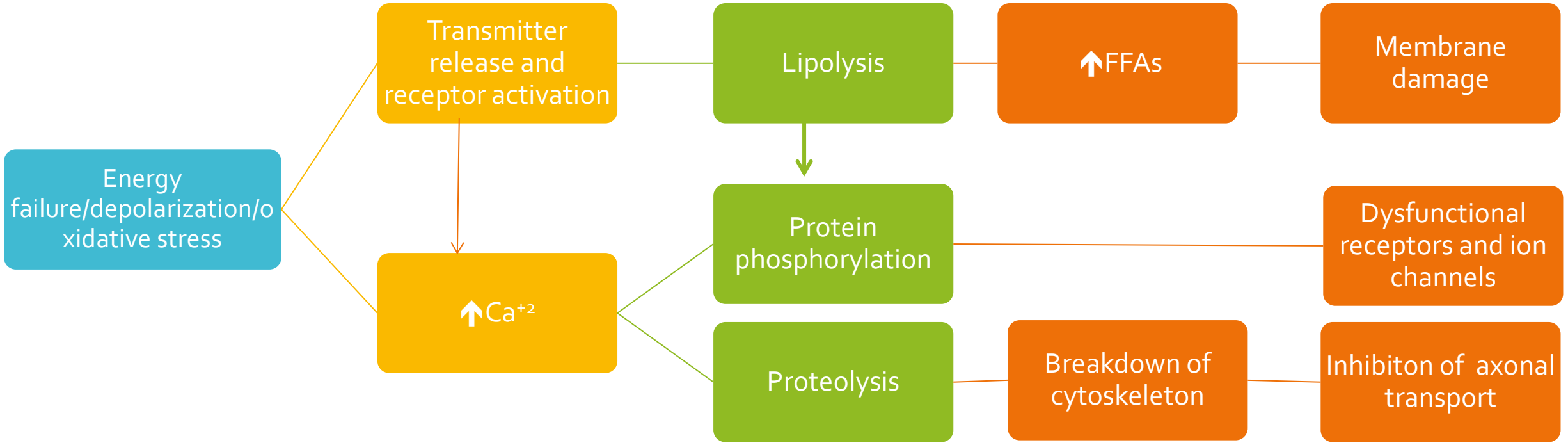
Calcium channel block

Nitric oxide synthase inhibitors and free radical inhibiton

Caplian inhibitors

Extra:
The goal of management in CVA is to evaluate and assess the patient within 6omins of arrival to minimize complications.
The treatment greatly depends on the underlying cause (hemorrhage or thrombosis). For more guidelines;
http://emedicine.medscape.com/article/1159752-overview

Consequences of brain ischemia



Questions

1- Which one of the following is an antioxidant:

A. Catalase
B. Hydrogen peroxide
C. Super oxide

2-Which of the following is a beneficial type of NOS

A. iNOS
B. nNOS
C. eNOS

3- Which of the following induces Calpain:

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

Answers :
1-A
2-C
3-B

Biochemistry
Team

If you find any mistake, please contact us:)

Biochemistry team leaders:

Basil AlSuwaine And Manar AlEid

Biochemistryteam@gmail.com