



**ETIOLOGY AND
PATHOGENESIS
OF
HYPOXIC-ISCHEMIC
ENCEPHALOPATHY**

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Hypoxic-Ischemic Encephalopathy

Encephalopathy due to hypoxic-ischemic injury [Hypoxic-ischemic encephalopathy (HIE)] is defined as brain injury caused by the combination of inadequate blood flow and oxygen delivery to the brain.

AAP and ACOG;

Encephalopathy is an acute intrapartum event sufficient to cause neuronal injury evidenced by :

- Metabolic acidosis (pH <7.0 and base deficit ≥ 12) in fetal umbilical cord arterial blood ,
- Need for respiratory support also starting in the first minutes,
- Low Apgar scores longer than 5 minutes.
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia)
- Multiorgan failure (eg, kidney, lungs, liver, heart, intestines)

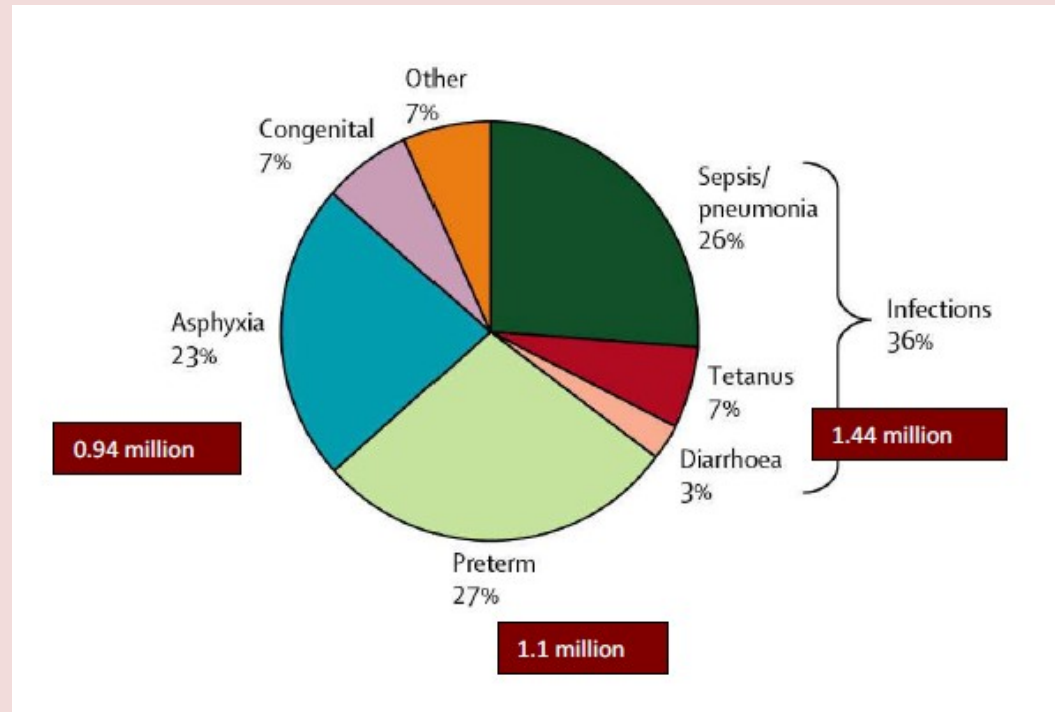
Hypoxic-Ischemic Encephalopathy

HIE in the World

-Major public health issue

-23% of the total 4 M deaths in the world

- In developed countries, moderate or severe HIE in 1 per 1000 live births.



Hypoxic-Ischemic Encephalopathy

Mortality between 10% and 60% of these infants with moderate or severe HIE die during the neonatal period.

At least 25% of the survivors have significant major long-term neurodevelopmental sequelae including MR, CP, and epilepsy.

Hypoxic ischemic encephalopathy is the primary cause of 15% to 28% of cerebral palsy among children.

Hypoxic-Ischemic Encephalopathy

Sequelaes of HIE

- Neurodevelopmental impairment
- Neuromotor impairments (CP)
- Mental retardation
- Epilepsia
- Behavioral and cognitive deficits
- Blindness and hearing loss
- Intellectual limitation,
- Language problems,

Shankaran S. Childhood outcomes after hypothermia for neonatal encephalopathy. NEJM. 2012

HIE - Etiology

Any condition that leads to decreased oxygen supply (hypoxia) and decreased blood supply to the brain (ischemia) can lead to this condition.

There is 5 mechanism that causes asphyxia/hypoxia in Newborn;

1. Interruption of umbilical blood circulation (Pathology of umbilical cord)
2. Impairment of placental gas exchange (Ablatio placenta, placenta previa)
3. Insufficient maternal side placental perfusion (Maternal hypo/hypertension, abnormal uterine contractions)
4. Impairment of maternal oxygenation (Cardiovascular and pulmonary diseases, severe anemia)
5. Insufficient pulmonary expansion and persistent fetal circulation (Severe



HIE - Etiology

	MATERNAL RISK FACTORS	FETAL RISK FACTORS
A N T E P A R T U M	<ul style="list-style-type: none"> - Endocrine diseases (diabetes vs) - Hypertension, Cardiovascular diseases - Epilepsia - Preeclampsia - Drug addiction - Drugs (lityum, MgSO4, reserpine) - Last trimester bleeding, Profound anemia - Mothers age (>35 years) - Multiparity, Severe infections 	<ul style="list-style-type: none"> - Twins, triplets - Postmaturity - Prematurity - Intrauterin growth retardation - Congenital anomalies - Fetal infections - Fetal anemia - Fetal dysthrythmias
I N T R A P A R T U M	PLACENTA AND CORD	OTHER RISK FACTORS
	<ul style="list-style-type: none"> - Ablatio placenta - Placenta previa - Small placenta - Prolapsus of umbilical cord - Tight nuchal cord - Cord anomalies - Umbilical vein/arterial anomalies 	<ul style="list-style-type: none"> - Abnormal presentations - Cesarian section - Vacuum/Forceps application - Premature rupture of membranes - Meconium stained amniotic fluid - Accelerated birth (<30 min) - Prolonged birth (>2 hrs) - Birth induction - Sedatives use
P O S T P A R T U M	RISK FACTORS	
	<ul style="list-style-type: none"> - Serious pulmonary diseases (Meconium aspiration, RDS, Pneumonia) - Congenital heart diseases - Sepsis and shock - Recurrent apnea - Serious congenital anomalies - Neuromuscular diseases - Prematurity - Severe anemia - Cardiovascular collaps (sepsis, severe blood loss, adrenal hemorrhage) 	

HIE - Pathophysiology

Cerebral injury and neuronal death

The underlying pathophysiology of perinatal HIE is difficult to study in the human, thus the neonatal rat model for HI brain injury has been developed to model this human condition.

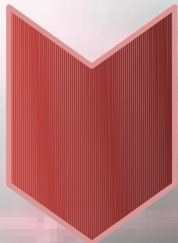
Much of what we know is derived from studies conducted in animal models.

HIE - Pathophysiology

Encephalopathy results from decreased oxygenation of the heart leading to hypoxemia, acidosis, and cardiovascular compromise in the fetus.

Initially, the fetus is able to compensate asphyxia by increasing cardiac output and blood flow to all organs.

As hypoxia becomes greater, the fetus redistributes blood flow to the heart, brain, and adrenals and does this by increasing vascular resistance in the periphery and decreasing vascular resistance in the heart and brain.



• **Hypoxic-ischemic insult**



• **Increase in cardiac output**
• **Blood flow increased to all organs**



• **Redistribution**
• **Blood directed to vital organs**



• **Cardiac output falls, hypotension occurs**
• **Neuronal injury and neuronal death occurs**

HIE - Pathophysiology

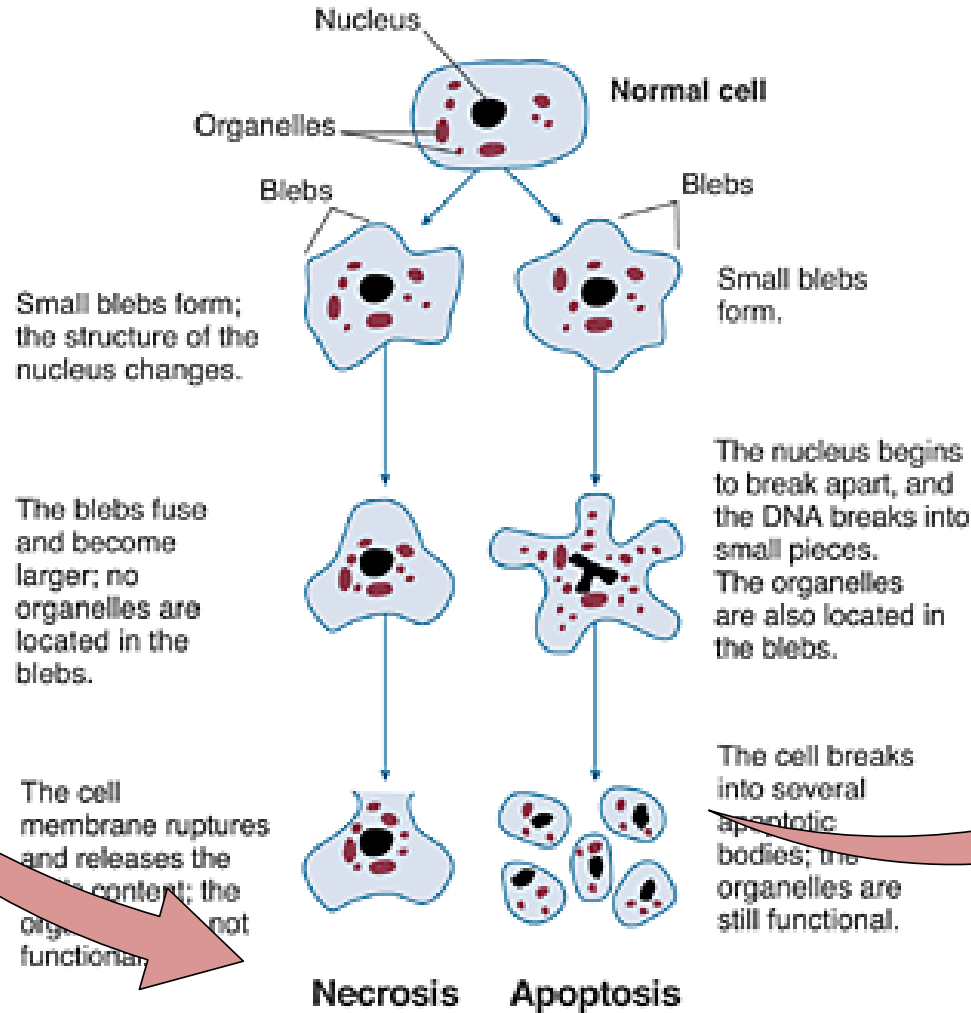
Hypoxic-ischemic injury leads to a biphasic pattern of encephalopathy and neuronal cell death;

-The first cells to die do so during or soon after the initial insult and this loss is termed ***“primary neuronal death”*** (Primary energy failure),

-The second form of cell death occurs some time after the initial insult and is termed ***“secondary”*** or ***“delayed neuronal death”*** (Secondary energy failure).

HIE - Pathophysiology

**PRIMARY
NEURONAL
DEATH**



**SECONDARY
NEURONAL
DEATH**

HIE - Pathophysiology

Primary phase

If the hypoxic-ischemic global insult is severe, and if uninterrupted, the insult results in exhaustion of high-energy metabolism (Primary energy failure) and immediate “primary neuronal death” (Necrotic cell death).

During the period of hypoxia-ischemia and the immediate phase of reperfusion, the key damaging processes involved are;

-Cellular energy failure,

-Excitotoxicity,

-Free radical damage and.

HIE - Pathophysiology

Primary phase, precludes oxidative phosphorylation, switch to anaerobic metabolism and leads to depletion of high-energy phosphate compounds such as ATP followed by accumulation of lactate and a fall in intracellular pH.

In response to a switch to this anaerobic state, glycolysis becomes the sole source of ATP production in the brain.

Oxidative phosphorylation; Produces 36 molecules of ATP for every molecule of glucose consumed,

Glycolysis; Generates only 2 molecules of ATP per molecule of glucose consumed.

HIE - Pathophysiology

An initial decrease in ATP results in neuronal membrane depolarization and loss of membrane ionic homeostasis.

At least 50% of brain metabolism is used to maintain ion gradients in neurons. Pumping Na^+ across the cell membrane is by far the most important energy-requiring process in the brain.

Failure of the ATP-dependent Na^+/K^+ ATPase pump leads to depolarization of cells, allowing the influx of sodium (Na^+), and a lesser efflux of potassium (K^+) with passive influx of chloride (Cl^-) and water into the cell.

The cellular swelling associated with the influx of water is known as osmotic (cytotoxic) edema, which may lead to necrotic cell lysis.

HIE - Pathophysiology

Also in hypoxic-ischemic insult, a massive accumulation of excitatory aminoacids, such as aspartate and glutamate, occurs by two ways; Release of glutamate into the synaptic cleft by the aid of efflux of potassium and failure of energy-dependent reuptake.

The increase in extracellular glutamate concentration and activation of glutamate receptors triggers excitotoxic cascade. Excess glutamate promotes further influx of water by opening Na^+/K^+ channels via the AMPA receptor, as well as Ca^{+2} influx via the NMDA receptors.

Also intracellular calcium accumulation occurs due to the failure during hypoxia of the energy-dependent process of calcium removal by the $\text{Na}^+/\text{Ca}^{+2}$ pump.

HIE - Pathophysiology

The rise in intracellular Ca^{+2} promotes;

-Free radical production,

-Nitric oxide (NO) production,

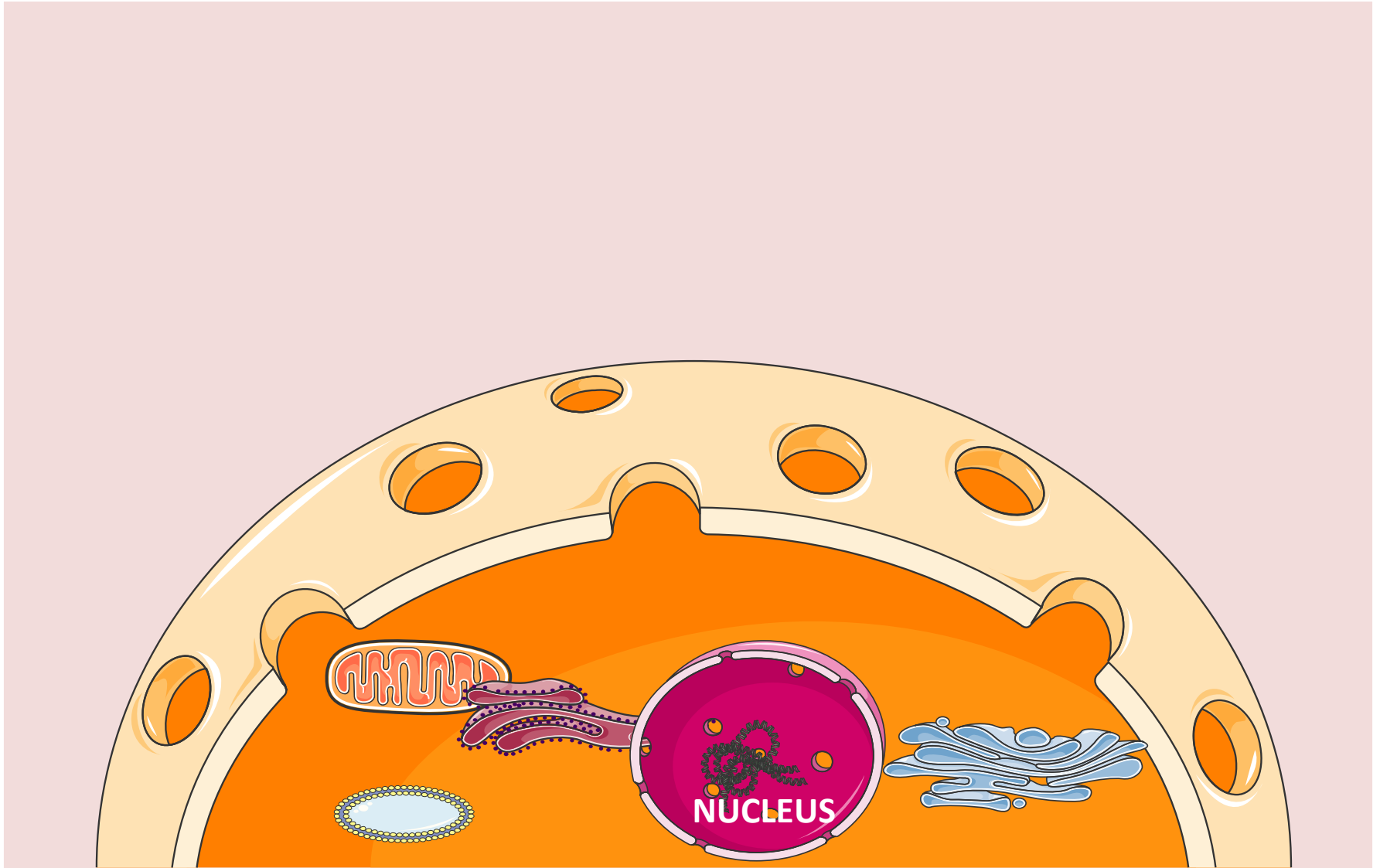
-Cell membrane damage, and

-Trigger of genes involved in apoptosis.

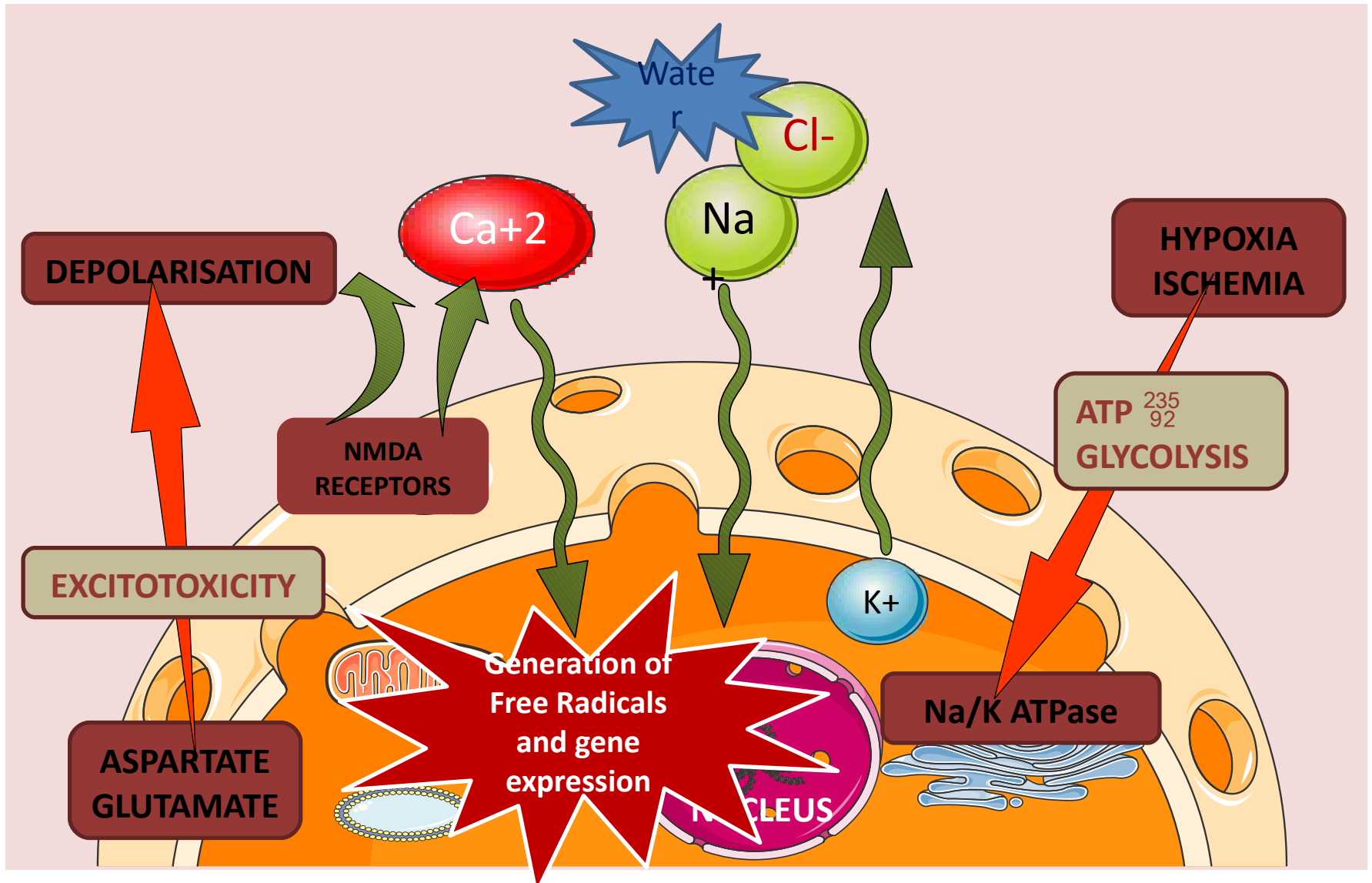
If primary hypoxic insult severe enough, neuronal necrosis can occur.

Primary phase is a prerequisite for all subsequent deleterious events.

HIE - Pathophysiology



HIE - Pathophysiology



HIE - Pathophysiology

Latent phase

However, many neurons don't die during the primary phase of neuronal death. Rather, a cascade of pathologic processes is triggered and leads to further loss of neurons, starting some hours later and extending over several days.

Reperfusion of the ischemic brain with successful resuscitation is followed by a “**latent phase**” of at least 6 hours (6 to 72 hours) when energy levels “*pseudo-normalise*” before the secondary energy failure and delayed neuronal death begin.

Restoration of cerebral blood flow, oxygen, and glucose delivery, the concentration of extracellular metabolites and intracellular pH normalizes with

HIE - Pathophysiology

This phase correspond to a therapeutic window for neuroprotective interventions to rescue the neurons that have been reversibly injured after the acute insult.

The reperfusion is necessary for the reversal of deleterious events leading to necrotic neuronal death during the primary phase of injury; however, the brain has not recovered from the initial injury and reperfusion can simultaneously cause additional (delayed) injury and mitochondrial dysfunction continues.

The neonate's body releases endogenous inflammatory cells and mediators following the initial injury that contribute to ongoing brain injury in the secondary phase.

HIE - Pathophysiology

Secondary phase

The secondary phase of brain injury does not occur in all infants with perinatal asphyxia and is primarily determined by several factors, such as duration and severity of hypoxic-ischemic insult, preconditioning events, substrate availability, body temperature, and gestational maturation.

The secondary phase of injury occurs slowly (hours to days) with a normal intracellular pH and stable cardiorespiratory status.

HIE - Pathophysiology

Secondary phase is characterized by;

- Decrease in the ratio of phosphocreatine/inorganic phosphate leading to a secondary energy failure, and cytotoxic oedema
- Accumulation of extracellular glutamate and excitotoxicity,
- Increase in cytosolic Ca^{+2} ,
- Generation of free radicals and NO
- Activation of phospholipases,
- Activation of caspase enzymes, and
- Microglial activation.

HIE - Pathophysiology

Proteolytic enzymes, especially caspases or cysteine proteases, will eventually trigger cellular nuclear fragmentation and mitochondrial damage.

Signals released from damaged mitochondria lead to apoptosis or programmed cell death as long as energy supplies persist.

The combined effects of cellular energy failure, acidosis, glutamate release, intracellular Ca^{+2} accumulation, lipid peroxidation, and nitric oxide neurotoxicity serve to disrupt essential components of the cell with its ultimate death.

HIE - Pathophysiology

Mechanisms of damage in the fetal/neonatal model of hypoxia-ischemia

Primary energy failure

- Decrease in CBF, O₂ substrates, high-energy phosphate compounds
- Excitotoxic-oxidative cascade
- Loss of ionic homeostasis across membranes, entry of intracellular calcium, mitochondrial disruption, brain acidosis, necrosis

Secondary energy failure

- Continuation of excitotoxic-oxidative cascade

Activation of microglia, inflammatory response

HIE - Pathophysiology

STAGES OF HYPOXIC-ISCHEMIC INJURY

PRIMARY PHASE

- Decrease in CBF, O₂ substrates, ATP
- Excitotoxicity
- Membrane depolarisation
- Intracellular Ca[↑],
- Mitochondrial disruption, -Cell lysis

REPERFUSION

LATENT PHASE

6-72 hrs

THEUROPATHIC WINDOW

SECONDARY PHASE

3-10 days

- Excitotoxic-oxidative cascade
- Activation of microglia-inflammatory response
- Activation of caspase proteins
- Reduction in levels of growth factors, protein synthesis
- Apoptosis-necrosis continuum