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THE ROLE OF ASTROCYTES IN STROKE

INTRODUCTION: WHAT IS STROKE?

Stroke is the result of a permanent or transient focal occlusion or rupture of a major brain artery or one of its branches. Is a leading cause of disability and death worldwide, affecting almost 800,000 people every year in the United States alone. Eighty-seven per cent of strokes are **ischemic**, in which blood flow to the brain is reduced; the remaining 13% are **haemorrhagic**, in which a vessel ruptures and blood accumulates in the brain. From many years researchers was focusing in neurons as a treatment target, but at the present time most of them are trying to understand how important could be the astrocytes in this kind of pathologies. The objective of this review is to understand which is the role of **astrocytes** in **stroke** and which functions play in this pathology and, finally, to discuss whether these functions are beneficial or harmful for brain.

STROKE'S PHYSIOPATHOLOGY

Stroke is caused by an interruption of cerebral blood flow that leads to stress, cell death, and inflammation. In general, stroke cascade is characterized by the following events: bioenergetic failure, acidotoxicity, excitotoxicity, oxidative stress and inflammation.

Nevertheless, has stroke an ordered disease? There are any phases, or all happens at the same time? The answer is that stroke has a timeline made up by threes phases:

- **Acute phase**, within a few minutes after stroke is beginning; terminal depolarization of cell membranes.
- **Subacute phase**, within 4–6 hours; molecular cell injury, the infarct core expands into the peri-infarct penumbra
- **Delayed phase**, several days to weeks; vasogenic edema, inflammation and possibly programmed cell death

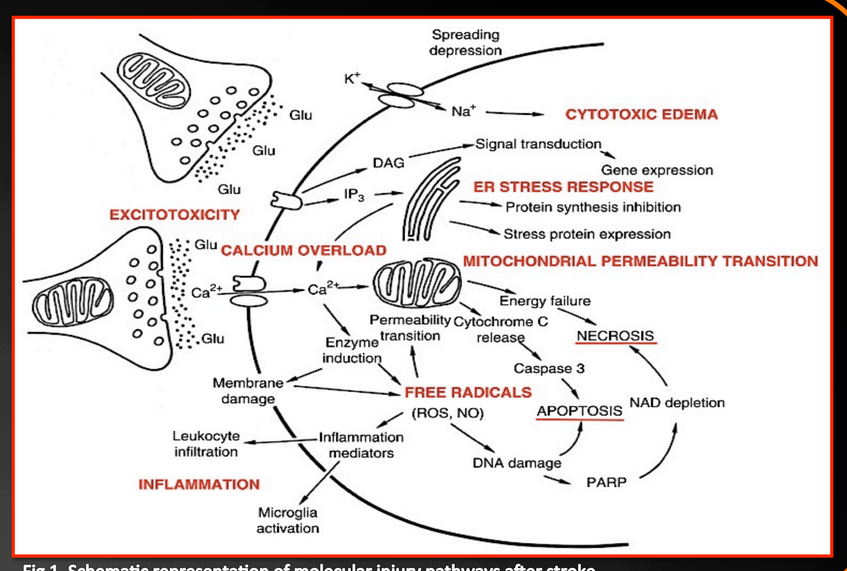


Fig 1. Schematic representation of molecular injury pathways after stroke.

OXIDATIVE STRESS

Low levels of oxygen favours the glycolytic pathway such as anaerobic ATP production. The result is an accumulation of lactic acid ending in acidosis which promotes pro-oxidant and detrimental changes in neurons.

- Astrocytes produce a number of antioxidants like Metallothioneins.
- Nrf2 specifically in astrocytes stimulates the transcription of antioxidant genes
- Astrocyte specific overexpressing of heat shock protein 72 or superoxide dismutase 2.

Astrocytes provide neurons antioxidants protecting them about oxidative stress

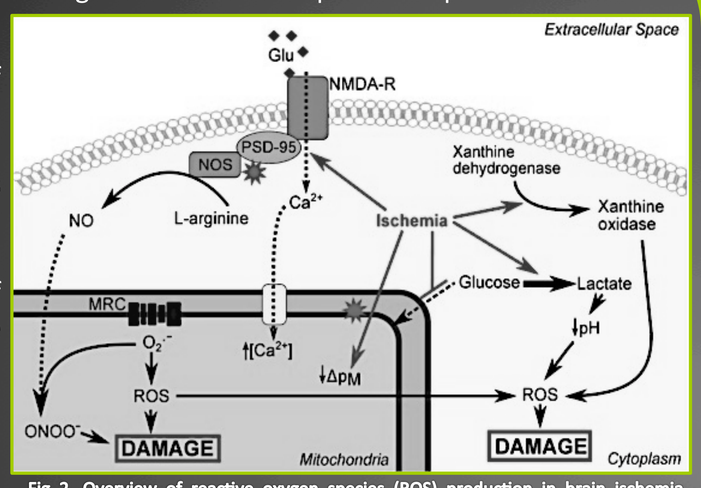
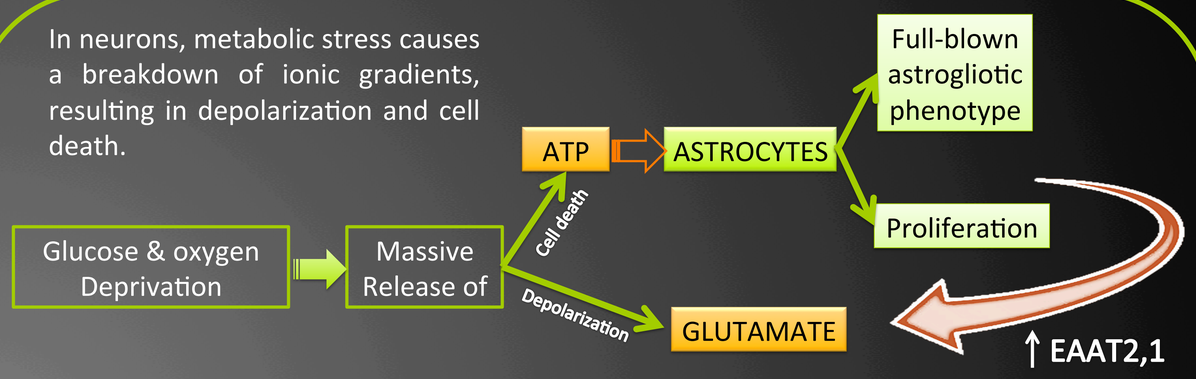


Fig 2. Overview of reactive oxygen species (ROS) production in brain ischemia. Accumulation of lactate as an anaerobic product of glycolysis, result in increased levels of superoxide conversion to other ROS.

METABOLISM & GLUTAMATE REGULATION

In neurons, metabolic stress causes a breakdown of ionic gradients, resulting in depolarization and cell death.



- Astrocytes react to ATP with hypertrophy, swelling of the cell body and main processes, and proliferation that ultimately result in full-blown astrogliotic phenotype.
- Astrocytic glutamate transporters (EAAT2, 1) can buffer and sequester glutamate, reducing excitotoxicity.
- Astrocytes will transform glutamate in glutamine to stopping the neural hyperactivity.

Astrocytes may provide partial protection from excitotoxicity and peri-infarct damage

ASTROCYTES RESPONSE?

INFLAMMATION

production and release of pro-inflammatory cytokines, such as tumour necrosis factor-α, chemokine, interleukins… by activated cells including **astrocytes**, microglia, neurons and endothelial cells, ends in neuronal and glial cell death during cerebral ischemia.

Pro-inflammatory cytokines can also induce the expression of adhesion molecules that are crucial for the infiltration of immune cells.

- Immune cells provide a defence against the invasion of pathogens
- inflammation is also involved in clearing damaged tissue, in angiogenesis, tissue remodelling and regeneration
- High levels of cytokines and chemokine can induce apoptosis of neuronal cells and/or increase toxic nitric oxide levels, inhibite neurogenesis…
- Astrocytes actively surround and segregate inflammatory and fibrotic cells

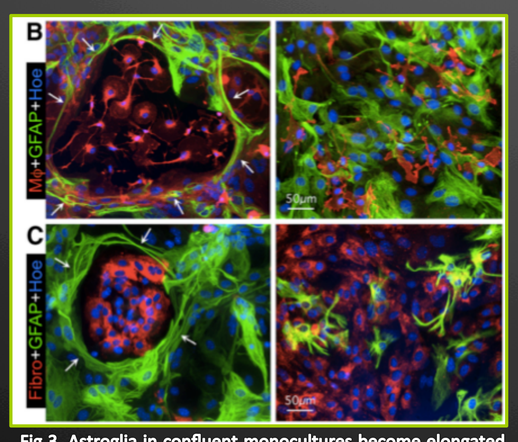


Fig 3. Astroglia in confluent monocultures become elongated and reorganize to surround newly added meningeal fibroblasts or macrophages in a STAT3-dependentmanner. *In vitro* multicolor fluorescence imaging of immunostaining of GFAP (astrocyte marker), Hoech (nucleus), CD45 (MΦ, macrophages), fibro (fibronectin). Right, wild-type. Left, KO-STAT3.

Activated astrocytes release cytokines and chemokine to notify the immune system the injury, but in the other side surround and segregate immune cells

REACTIVE ASTROGLIOSIS & SCAR FORMATIOM

Activate: Transforming growth factor-alpha (TGFα), cilliary neurotrophic factor (CNTF), interleukin-6 (IL-6), leukeamia inhibitory factor (LIF), oncostatin M…

Forms: **Reactive astrogliosis:** complex and gradated process, firstly is ranging from minor changes in gene expression and ends in cell hypertrophy to astrocyte proliferation and scar formation.

Astroglial scar: is composed by chondroitin sulphate proteoglycans (CSPG), astrocytes, microglia and macrophages.

- Barrier function against pathogens and immune system cells.
- Delimit toxic effects on adjacent tissue
- inhibits axonal growth and other repair processes

Reactive astrogliosis it is a graded process which forms an astroglial scar. The scar makes a barrier, delimits toxic effects and inhibits axonal growth

BENEFICIAL OR HARMFUL RESPONSE?

- Astrocytes play many **beneficial roles** in stroke: reduce neurotoxicity oxidative stress, maintain the energy levels in neurons, notify the immune system, stop the inflammation and scar formation avoids the injury and inflammation progress.
- In delayed phase astroglial scar play a **harmful role** because it does not let synaptogenesis formation.

Astrocyte response is essential in a stroke. Nonetheless, in delayed phase scar formation inhibits axonal growth, which is important for the patients' recovery. So, in futures studies would be important study how stop the scar formation once the injury is controlled.

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