Establishing the neurovascular unit's chronology in ischemic stroke's onset

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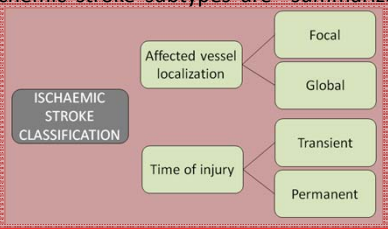
I. CONTEXT AND INTRODUCTION

- The term *Stroke* or *cerebrovascular accident* refers to the sudden death of a cerebral tissue area due to lack of oxygen when the blood flow to the brain is impaired by blockage or rupture of a cerebral artery.
- According to the World Health Organization data, stroke is the second cause of death worldwide, being responsible approximately of the 12% of worldwide deaths every year.
- In Pathology field, different **types of stroke** are defined according to it causes or consequences:
  - **Hemorrhagic** stroke -> Vessel rupture inside the Central Nervous System.
  - **Ischaemic** stroke -> Blockage of cerebral blood flow or oxygen supply to the brain. Ischemic stroke subtypes are summarized in the following schema:



II. AIMS

The main aim of this project is to establish an approximate chronology of the different physiological, tissular and cellular events which take place in the neurovascular unit within the situation of an ischemic stroke.

III. MATERIALS AND METHODS

In this review project either most recent publications or classical ones related to the neurovascular unit and its response to ischemia were studied:

- Firstly a search of terms *neurovascular*, *ischemic stroke* and *endothelial responses* was held in *Pubmed* and *ScienceDirect*, and the articles found were ordered by preference and impact.
- Secondly the articles considered most relevant or important were read and summarized and their bibliography extensively analyzed.
- Eventually a graphical representation of neurovascular unit implications in ischemic stroke was made in order to summarize all the information found.

IV. NEUROVASCULAR UNIT AND ITS RESPONSE TO ISCHAEMIA

Neurovascular unit (NVU) (concept) derives of a big number of observations which reported how vascular elements, supporting compounds and neuronal cells work together in order to achieve the complete protection and metabolic regulation that brain needs at any time.

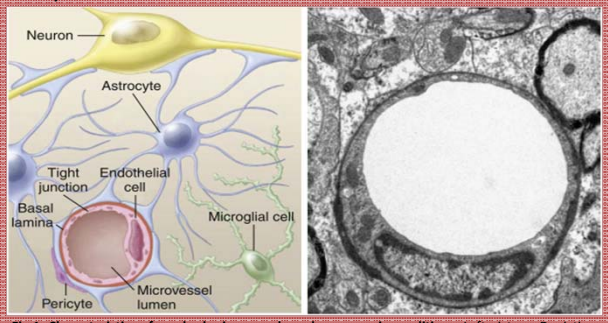


Fig.1. Characteristics of cerebral microvessels under normoxic conditions. Left picture: Depiction of neurovascular unit displaying relationships between neurons and their supply capillaries. Right picture: Capillary from rat inferior colliculus. Note endothelial cell, basal lamina matrix, and surrounding astrocyte end-foot. 4.5-5.0 µm diameter. Adapted from del Zoppo and Hamann, 2011.

The diagram below illustrates different cellular elements interacting with endothelium in the normal NVU.

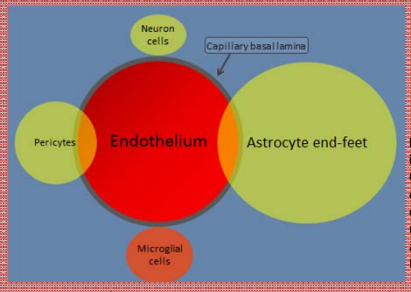


Fig.2. Schematic representation of cell interaction in the neurovascular unit. Cellular elements are shown in yellow, endothelium in red, immune system in orange, basal lamina in grey and extracellular matrix in blue. An interaction is more frequent as more overlapped are the circles. Infograhy by the author.

Every one of those elements is capable of regulating endothelium physiology in the NVU by releasing a wide range of metabolic mediators, even though in normal conditions only astrocyte and pericyte influences are remarkable.

The NVU suffers changes and find its physiology perturbed from the very onset of ischemic situation. As a result of the research that has been done, all changes that NVU suffers due to ischaemia can be classified under the next four main tittles:

1. Loss of endothelial permeability barrier leading to perivascular edema establishment .
2. Loss, by enzymatic digestion, of the vessel basal lamina and extracellular matrix, leading to haemorrhagic transformation process.
3. Alterations in cell-matrix signaling systems, which would start a wide range of cytological changes as iniciating apoptosis-like cell death pathways.
4. Leukocyte adhesion receptors expression in endothelial surface , leading to neuroinflamation processes.

Neurovascular crhonology after ischaemia onset

As a result of the present study, a graphic representation of the chronology of neurovascular unit processes promoted by ischaemia has been made:

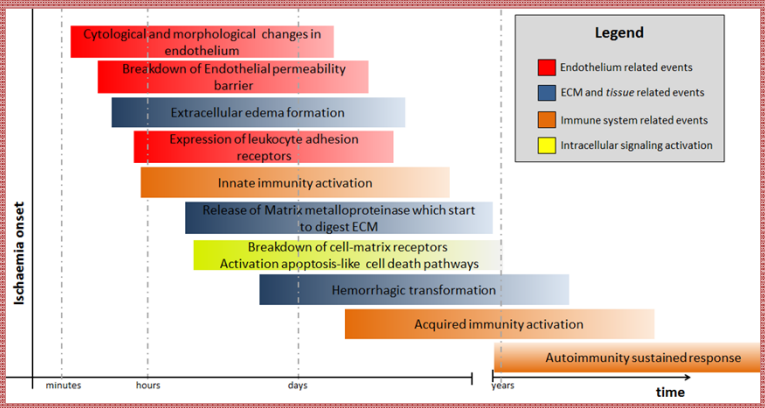


Fig.3.Graphic representation of ischaemia chronology in the neurovascular unit. Different colours show implication of different nature compounds in the neurovascular unit and its surrounding tissue. Infography by the author.

CONCLUDING REMARKS

- ✓ Neurovascular unit experiments alterations from the very instant that ischaemia is established.
- ✓ The neurovascular unit disengagging is the most clear red line in ischaemic stroke, leading to the start of infarction and irreversible tissue injury.
- ✓ New pharmacological strategies should target the basal lamina of cerebral capillaries in order to protect it from digestion.

CREDITS FROM FIGURES:

Figure 1: Del Zoppo, G. J., & Hamann, G. F. (2011). *The Cerebral Microvasculature and Responses to Ischemia*. *Stroke* (Fifth Edit.). Elsevier. doi:10.1016/B978-1-4160-5478-8.10002-8

Figures 2 and 3: Infography by the author.