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Editorial

Cyto-Neurology in Ischemia

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Neurons are classically considered the most important cells of nervous system and their major function is to enable communication within this complex system [1]. This is done by means of action potentials and synaptic transmission, which are only possible due to the shift in the membrane potential caused by the flow of ions through the neuronal membrane [1]. To maintain the ideal ionic gradients, it is necessary to have a constant supply of oxygen and glucose, and any imbalance threatens neuronal functions [1]. These intrinsic neuronal characteristics, and the fact that neurons do not have their own energy stores, makes them the most sensitive cells of human body to ischemia [1].

The trigger of all ischemia-induced detrimental effects is the oxygen and glucose deprivation caused by the reduction of blood flow [1]. Initially, neurons depend on the availability of alternative glycolytic and oxidative substrates and on the rate of ATP consumption [2]. Whereas glucose metabolism is a primary source of cellular energy, oxygen is mandatory for mitochondrial respiration to produce ATP; oxygen deprivation immediately and severely reduces ATP production, resulting in a rapid decrease of their levels due to ongoing consumption [2]. Furthermore, the disruption of oxidative phosphorylation triggers ATP synthase to run backward and consume ATP (increasing its loss) and to produce electron leak, which enhances the production of reactive oxygen species (ROS) [2]. Finally, when respiration is inhibited but glycolysis persists, protons and lactate generated during glycolysis accumulate, causing rapid intracellular acidification [2].

The decrease in the available energy and the intracellular acidification trigger several detrimental mechanisms, such as the loss of ion pump function, the release of excitatory neurotransmitters, and oxidative stress, all of which are promoters of neuronal death [1,2]. The loss of ion pump function is associated with an efflux of potassium and an influx of sodium, chloride, and calcium ions, thereby modifying the ionic gradients in the intracellular and extracellular compartments, which, if not reversed, in time will lead to necrosis [1,2]. Additionally, the increase in intracellular calcium also leads to the activation of apoptotic pathways and to the release of excitatory neurotransmitters such as glutamate [1]. After ischemia, the release of glutamate is associated with a dysfunction in the reuptake mechanism because of ion-gradient dissipation [1,2]. This results in glutamate accumulation in the synaptic cleft leading to the overactivation of glutamate receptors, a phenomenon known as excitotoxicity [1]. Oxidative stress is another step in the ischemic cascade and is caused by the production of ROS [1,2]. These radical species react with and damage almost all neuronal components, causing biochemical, functional, and metabolic abnormalities, which ultimately trigger apoptotic mechanisms as shown in Fig. 1 [1,2].

Unfortunately, ischemic stroke (IS) is a major cause of death and disability worldwide, being responsible for about 87% of all strokes [3]. In addition to the neuronal death described, after ischemia there are also other local detrimental effects, such as the increase of inflammation and damage of other components of the neurovascular unit, such as the loss of permeability of the blood brain barrier [3].

The ischemic penumbra is the area located between the infarct core and healthy brain tissue [4]. Cells in the penumbra are salvageable if reperfusion is established during the early hours after the ischemic event [4]. Most current therapeutic strategies focus on the preservation of the penumbra, which can potentially reduce the infarct area and significantly attenuate the neurological dysfunctions of IS patients [4].

It seems clear that the neuronal failure triggered by the ischemic cascade involves several cellular pathways and structures, raising the idea that to recover the penumbra neurons, strategies should be used that have an integrative approach by modulating several of the above-mentioned detrimental effects. Among the several brain-repair-based therapies that have been proposed, repetitive transcranial magnetic stimulation (rTMS) has shown promising results by preventing apoptosis, neurite rupture, and inflammation,

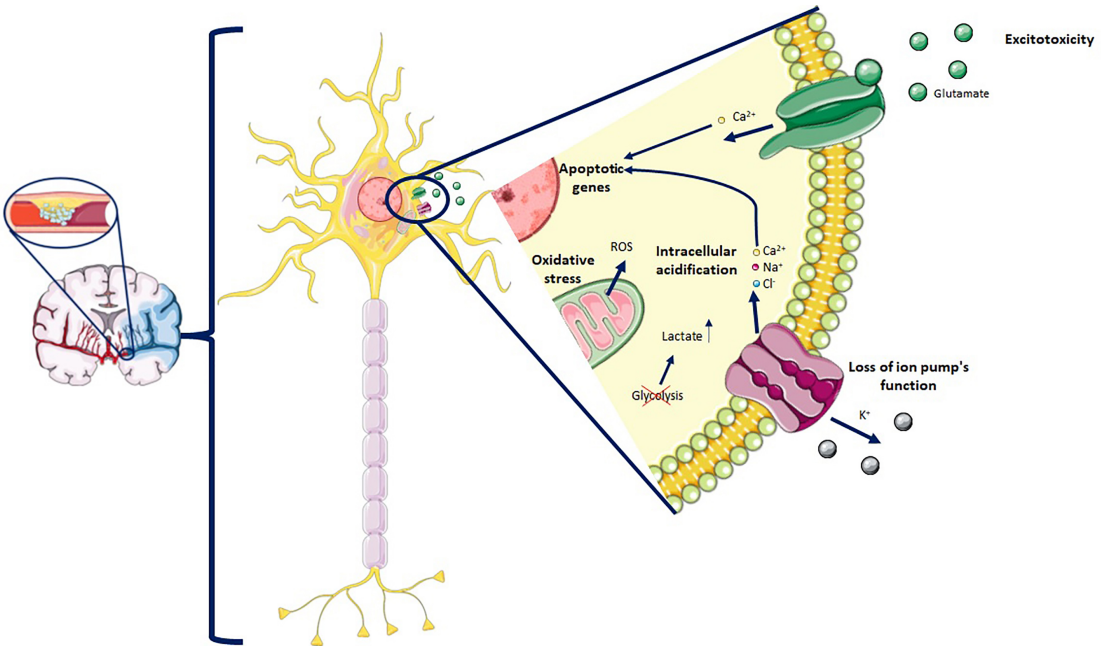

Fig. 1. Ischemia-induced neuronal detrimental effects.

as well as by increasing neuroprotection, neurogenesis, and synaptic plasticity in several animal [5] and cellular models [6]. Those effects are correlated with an improvement of neurological, motor, learning, memory, and cognitive deficits, as reviewed by Zong and colleagues 2022 [5].

Targeting inflammation has been regarded as another goal in the reduction of brain damage in acute stroke. Although dampening innate immune responses and addressing complement or danger signaling effectively reduces acute brain damage [7], certain inflammatory responses are actually necessary for repair because they induce cell migration, proliferation, matrix deposition and tissue remodeling [8]. This suggests that initial inflammatory reactions trigger a set of responses that may also improve functional outcome in the long term [8].

The last decade has brought tremendous advances in therapeutic options for cerebrovascular diseases, as evidenced by the development of thrombectomy in IS, which benefits an increasing number of patients and eventually facilitates the way for a reappearance of neuroprotectants. The search for effective cerebroprotectants requires an efficient and valid experimental paradigm. Candidate agents may emerge from a better understanding of mechanisms such as the molecular and cellular pathophysiology of ischemia as well as agnostic pharmacological screening [9].

Currently, only a few potential cerebroprotectants are under evaluation in human trials. Instead, the focus of interest has been directed toward nonpharmacological treatments such as remote ischemic conditioning and rTMS, and there is evidence of growing interest in pleiotropic agents that act via multiple or even unknown mechanisms [3]. The efficacy of conditioning for acute IS is being reviewed and, although there is still no firm conclusion that it benefits patients, more promising clinical trials are being carried out [10]. Among others, some examples of pleiotropic therapies under study for stroke include therapeutic hypothermia [11], APC (activated protein C) analogs [12], targeting neuroinflammation [7,8], and the use of exosomes [13] and microRNAs [14].

Many stroke researchers have seen the failure of large clinical trials of neuroprotective treatments and the celebration of the triumph of therapies like recanalization, thrombolysis, and thrombectomy [15]. Moving ahead, success in developing brain protection, either as an adjunct to recanalization or as a stand-alone treatment, will require a new approach based on understanding the importance of differential vulnerability in the neurovascular unit [15].

Author Contributions

Both authors contributed equaly to the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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