Editorial

Critical Appraisal of Ischemic Stroke Pathophysiology: Road to Cerebral Resuscitation? Part I

Acute ischemic stroke is the most common cerebrovascular disease and a leading cause of long-term disability, mortality and human suffering. The most common cause of ischemic stroke is sudden occlusion of a blood vessel, eventually leading to the death of neuronal, glial, and endothelial cells. Current knowledge regarding the pathophysiology of cerebral ischemia indicates that the mechanism of neuronal injury is multifactorial in nature that include metabolic stress, ionic perturbations, oxidative stress, excitotoxicity, calcium overload, blood-brain barrier disruption, inflammation and necrosis/apoptosis. The theme of this special issue is inspired by the marked rise of scholarly research in the area of ischemic stroke in recent years. This carefully compiled two-part thematic issue provides a general overview and update of various signaling pathways in the development of cerebral infarct during an ischemic event. The selected review articles not only provide an overview of current open issues, but also identify potential lines for further research in the area of ischemic stroke. Part 1 focuses on the recent findings on ischemic stroke pathophysiology with special emphasis on inflammation and sheds light on the existing and emerging treatment concepts.

Factors regulating coagulation and fibrinolysis have been in the focus of stroke treatment for a long time. However, the risk of inducing hemorrhages poses an important safety concern. Thrombomodulin (TM) is a membrane protein mainly expressed by endothelial cells. It is part of the anticoagulant protein C system but recently several effects were discovered which occur independently of protein C activation. Along this line, the contribution by Jan Wenzel, Julian Christopher Assmann, and Markus Schwaninger attempts to provide an overview about the functions of TM and highlights the potential protection provided by TM during and after ischemic periods, in particular its influence on stroke mechanisms. Further, their review is based on recent preclinical and clinical studies of TM function.

The cellular components of brain and the cerebral vasculature are located in close proximity to each other. This functional unit is termed as the 'neurovascular unit' (NVU) and there is growing recognition that any disruption of these complex interactions may lead to NVU dysfunction during neurodegenerative conditions including brain ischemia. In their review, Yasukazu Terasaki, Yi Liu, Kazuhide Hayakawa, Loc-Duyen Pham, Eng Lo, Xunming Ji, and Ken Arai attempt to explore how cell-cell interactions within the NVU, especially in non-neuronal cells, can modify and amplify these pathophysiologic mechanisms by affecting the ability of NVU components to regulate signaling mediators such as glutamate, free radicals, growth factors, cytokines, chemokines and extracellular vesicles.

In the next article, Naijian Chao and Sheng-tian Li survey a series of synaptic and extrasynaptic glutamate signaling cascades that lead to neuronal death and cerebral injuries during ischemic stroke. The article starts with an overview of recent discoveries on the glutamate receptors with an emphasis on the role of NMDA receptors in ischemic stroke. The authors then discuss the integrated glutamate signaling pathways in detail, setting their scope at both synaptic and extrasynaptic locations. Furthermore, they briefly review the role of astrocytes in extrasynaptic glutamate signaling, highlighting their potential in regulating glutamatergic processes.

Dysregulation of calcium is one of the major instigators leading to neuronal death and brain injury following ischemic stroke. The article entitled ‘Calcium ion – the key player in cerebral ischemia’, by Suvanish Kumar, Aswathi Gopalakrishnan, Nazıroğlu, and Rajanikant G K portrays calcium as one of the role players in neuronal death and cerebral damage following ischemia. The role of calcium in neuronal functioning, its regulatory mechanisms and the failure of homeostatic mechanisms are discussed in detail. The article emphasizes that further investigation of calcium influx and efflux pathways is prerequisite to enable the design of neurotherapeutics to positively modulate neuronal intracellular calcium levels following ischemia.

Inflammation following ischemic stroke is increasingly recognized as a key element in its progression. A comprehensive review contributed by Jong Youl Kim, Masahito Kawabori, and Midori Yenari focuses on the current findings pertaining to innate immune responses and mechanisms, and provides an update on the understanding of post-ischemic inflammation and possible therapeutic potentials. Further, this review describes the different key players in neuroinflammation and their possible detrimental and protective effects in stroke.

The next article entitled “Understanding the multifaceted role of inflammatory mediators in ischemic stroke” by Diana Amantea *et al.* is aimed at providing a better understanding of the dualistic role played by each component of the inflammatory/immune response in relation to the spatio-temporal evolution of ischemic stroke injury. Though the immunomodulation represents a promising therapeutic approach against ischemic stroke, most clinical trials aimed at targeting inflammation have failed to translate into Phase III. In this context, the authors emphasize the need for selective targeting of detrimental components of the inflammatory response to stroke for developing an effective treatment.

Having considered the role of thrombomodulin, calcium, inflammation, and topics related to mechanisms of neurovascular dysfunction and synaptic and extrasynaptic glutamate signaling in ischemic stroke in Part 1 of the theme issue, we will focus more specifically on the role of hypertension and microglial activation in ischemic stroke in Part 2.

G.K. Rajanikant
Guest Editor
School of Biotechnology
Coordinator, DBT - Bioinformatics Center
National Institute of Technology Calicut
Calicut 673601
India
Tel: +91 495 228 5452 (Off)
Fax: +91 495 228 7250 (Fax)
E-mail: rajanikant@nitc.ac.in

Etheresia Pretorius
Guest Editor
Department of Physiology
Faculty of Health Sciences
University of Pretoria
Private Bag X323, Arcadia
South Africa.
Tel: +27 12 420 2864
Fax: +27 12 420 4482
E-mail: resia.pretorius@up.ac.za