Handbook of Neurochemistry and Molecular Neurobiology

Acute Ischemic Injury and Repair in the Nervous System

Abel Lajtha (Ed.)

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Volume Editor: Pak H. Chan

With 55 Figures and 16 Tables

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Preface

Stroke is a global health problem affecting approximately 15 million people annually in the world and about 700,000 people in the USA. It is the third leading cause of death and the most common cause of disability in most developed countries. The majority of strokes are ischemic (the blood flow to the brain is blocked), whereas a small percentage of strokes are hemorrhagic (the blood vessels burst). The molecular and cellular mechanisms of neuronal death that lead to brain injury and infarction after ischemic stroke have been intensively investigated over the past several decades. These investigations have led to our current understanding of the neurobiology of the disease at the molecular and cellular levels and have provided an impetus for the development of therapeutic strategies to treat brain injury in patients after an ischemic stroke.

This volume is intended to provide state-of-the-art and the most up-to-date knowledge on the mechanisms of neuronal death and repair after stroke. It begins with an overview of gene expression profiling in ischemic brain injury and ischemic tolerance for identification of the genes/proteins that are involved in neuronal death and neuroprotection. This chapter is followed by major discussions by leading experts in the field on the chosen gene/protein candidates that may affect neuronal death and survival. These candidate proteins include apoptotic-inducing factor (AIF) and poly(ADP-ribose) polymerase-1 (PARP-1), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), endothelial nitric oxide synthase (eNOS), and neuronal nitric oxide synthase (nNOS). Activation or expression of these proteins is known to induce DNA damage that leads to neuronal apoptosis. A succinct overview of the mechanisms of DNA damage and repair in ischemic neurons follows.

Protein synthesis, folding, aggregation, and degradation are known to play major roles in mediating the fate of ischemic neurons and this aspect is discussed, followed by a chapter that describes the neuroprotective or apoptotic role of heat shock protein. The neurobiology of superoxide dismutase, the key endogenous antioxidant enzyme in free radical detoxification and signaling in neuronal death or survival after cerebral ischemia is reviewed, and this basic research provided mechanistic support to the recent success of spin trap NXY-059 in a clinical stroke trial.

The neurovascular unit, which consists of many cell types, and its interaction and integrity have recently evolved as prime targets for therapeutic intervention in stroke. Thus, the two chapters that describe the biology of glial and cerebral endothelial cells and their role in the integrity and repair of the neurovascular unit are of major importance. This is followed by reviews on sex steroids and gender in ischemic pathobiology and the mechanisms of ischemic cell death in the developing brain. A review of the molecular mechanisms of cell death following subarachnoid hemorrhage is presented. The basic molecular and cellular mechanisms of neuroprotection of the antibiotic minocycline, a potential therapeutic agent in clinical stroke, are clearly reviewed by experts in the field. This chapter is followed by the concluding chapter, an outstanding review of the roles of matrix metalloproteinases and tissue plasminogen activator in reperfusion therapy that target the neurovascular unit in stroke.

It is our belief that this volume provides an excellent review of the tremendous advances of the past decades in neurochemical and molecular biological aspects of cerebral ischemia. We hope that these advances, as communicated through this volume, will provide an impetus for basic scientists and clinicians to further their translational research and to promote the insights for development of therapeutic interventions for stroke.

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