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COMPARTMENTALIZED CAMP SIGNALING IN NEURODEGENERATIVE DISEASES

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Neurodegeneration is becoming a major health problem for ageing population worldwide. The high morbidity and mortality for neurodegenerative disorders demand earlier diagnosis and better taylored treatment. Neurodegeneration occurs as consequence of progressive deterioration of the neuronal structure and activity that eventually leads to neuronal dysfunction and cell death. Recent discoveries highlighted the existence of common mechanisms underlying the onset and progression of a variety of neurodegenerative disorders. Understanding the pathogenic mechanisms of neurodegenerative diseases and interfering with aberrant neural activity represent the principal aims of many investigators in the field. Reversible modification of proteins, such as phosphorylation and ubiquitination, are the most common and important modes to control protein function. In neurons, protein modification induced by the second messenger cAMP at subcellular compartments is emerging as a key mechanism to control the generation and dissemination of neutrophin signals from cell membrane to target substrates. Dysregulation of such a mechanisms could promote neuronal dysfunction and disease. Here, we will focus on the role of deranged cAMP signaling in neurodegenerative disorders.

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MAMMALIAN CARBONIC ANHYDRASE FAMILY OF ENZYMES IN THE NERVOUS SYSTEM: A FOCUS ON CARBONIC ANHYDRASE IX

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Mammalian carbonic anhydrases (CAs; also known as Carbonate Dehydratases EC 4.2.1.1) constitute a wide and complex family of enzymes, due to their peculiar schemes of expression and localizations in tissues and cells. Their fundamental activities are involved in transport of CO_2 and bicarbonate, pH balance, gas exchange, ion transport. However, besides their enzymatic activities, CAs are emerging as key regulators in several cellular processes. Among CAs, CA IX is a classical target of the hypoxia-induced factor HIF1A, ensuring proper response of cells to hypoxic stresses. Although CA IX is widely recognized as a prognostic factor and a therapeutic target in human cancer, its known properties, as well as its recently described novel activities, may be relevant to the physiopathology of the nervous system. In this review we describe the general properties of the several members of the carbonic anhydrase family of enzymes and their involvement in the physiopathology of the nervous system. We then conclude with a focus on the recently described, novel molecular functions of CA IX, highlighting the potential involvement of this peculiar member of the family in the neuronal responses and adaptation to hypoxic stress.

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MITOCHONDRIAL NCX3: A NEW PLAYER IN THE REGULATION OF MITOCHONDRIAL CALCIUM HANDLING IN NEURODEGENERATIVE DISEASES

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Mitochondria are intracellular membrane enclosed organelles found in most eukaryotic cells, which play important roles in several cellular functions, such as the production of energy by oxidative phosphorylation, the regulation of cellular calcium homeostasis, and the control of programmed cell death. The mitochondrial influx and efflux calcium pathways play a relevant role in cytosolic and mitochondrial calcium homeostasis and contribute to the regulation of mitochondrial functions. Furthermore, mitochondria are dynamic organelles that actively divide, fuse with one another, and undergo to regulated turnover, all of which are important for the maintenance of mitochondrial function and quality control. According to a widespread concept, neurons are critically dependent on mitochondrial integrity based on their specific morphological, biochemical, and physiological features. Indeed, neurons are characterized by high rates of metabolic activity and need to respond promptly to activity-dependent fluctuations in bioenergetic demand. The dimensions and polarity of neurons require efficient transport of mitochondria to hot spots of energy consumption, such as presynaptic and postsynaptic sites. Consequently, alterations in any of these mitochondrial features can potentially cause disease and have been linked to the pathogenesis of neurodegeneration. In this review particular emphasis will be devoted to the description of the role played by the newly identified mitochondrial proteins in the regulation of mitochondrial calcium dynamics as starting point for investigation of new molecular target responsible for mitochondrial dysfunctions leading to neuronal degeneration.

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POTASSIUM CHANNELS IN NEURONAL DEATH AND SURVIVAL

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Changes in the intracellular and extracellular concentration of several ion species have been shown to occur and to play a critical role in specific neurodegenerative diseases, and hyperactivation of glutamate receptors (excitotoxicity) appears as a primary mechanism for neuronal death occurring upon exposure to neurodegenerative stimuli. A large number of potassium channels are expressed in distinct neuronal type, each with specific biophysical, functional, and pharmacological properties; despite their role in controlling neuronal excitability has been widely explored, much less attention has been dedicated to investigating their participation in neuronal survival/death mechanisms. Therefore, the aim of the present work is to review the available preclinical data on potassium channels contribution in cell death triggered by various neurotoxic insults, and to provide explanations reconciling apparently contradictory conclusions present in the literature. Given that several new potassium channel modulators are currently being developed for the treatment of various neurological and non-neurological indications, it seems possible to envisage that these molecules may be optimized for the treatment of various neurodegenerative diseases where potassium channels specifically participate in disease pathogenesis.

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