

NITRIC OXIDE AND SPHINGOLIPIDS AS MODULATORS OF APOPTOSIS AND AUTOPHAGY: FUNCTIONAL IMPLICATIONS IN NEURODEGENERATIVE CHRONIC BRAIN DISORDERS

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Aberrant regulation of the apoptosis and autophagy machineries is a central abnormality in most human neurodegenerative disorders characterized by progressive dysfunction and death of neuronal and glial cells. Both in central and peripheral nervous systems, cell death can be either apoptotic or autophagic, depending on the cellular setting and inducing stressor. However, while some mixed phenotypes have been reported, apoptosis and autophagy ultimately may develop in mutually exclusive ways and appear to inhibit each other. Generation of the pleiotropic sphingolipid mediator ceramide is a key event in many cellular processes including survival and death, in which also the short-lived gaseous messenger nitric oxide (NO) plays a crucial role. Much progress has been made in understanding the crosstalk among the NO and the sphingolipid pathway, with its multiple feedback controls which have important implications in neurophysiological and neuropathological processes. Strikingly these mediators impact on both apoptosis and autophagy. What we provide here are details on how NO- and sphingolipid-dependent signaling impact on chronic brain disorders, i.e., Alzheimer's, Parkinson's, and Huntington's diseases; we also describe how their crosstalk and regulation of autophagy and apoptosis may play a significant role in determining the pathogenic evolution. The evidence we report suggest that targeting the NO and sphingolipid signalling pathways may ultimately be exploited in therapeutic perspective. However, defining how this integrated pathway balances towards beneficial vs. toxic effects appears to be complex and needs being resolved to identify suitable therapeutic targets and strategies.

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PROTEIN SILENCING WITH INTRACELLULAR ANTIBODIES: TARGETING ALZHEIMER'S DISEASE PROTEIN

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Despite intensive research, no generally accepted mechanism has yet been formulated causally linking the Alzheimer's disease (AD) triad (cholinergic deficit, amyloid A β and tau pathologies) into one unified conceptual scheme. A major current obstacle in the AD field is the lack of techniques to reliably validate targets relevant for the pathogenic mechanism. Indeed, a validated target is not just a well identified molecule. In order to be validated, and to become the object of a pharmacological intervention, targets need to be defined in their protein interactions, cellular context, post translational modifications, including quaternary structure and oligomerization state or conformers. This is true in general, for most human diseases, but even more so for neurodegenerative diseases. There is, therefore, the need for new approaches for target discovery and validation relevant for AD. Currently, much of the target discovery and validation arena exploits nucleic acid based approaches, such as transgenic approaches for gain of function studies, and gene knock-out or RNA interference for loss of function. The latter represent powerful technologies but, from the point of view of target validation, their predictive value is intrinsically limited, as they cannot access selectively the diversity of protein targets. This review article describes the so called intrabody technology (intracellular antibodies), whereby antibodies are used as genes, rather than as proteins, to achieve protein silencing in a spatially, temporally and molecularly defined manner. Antibodies represent a particularly promising class of reagents, because of their ability of potentially recognizing, in a highly specific manner, a virtually unlimited repertoire of protein antigens, including, for instance, the different pathological conformation intermediates of misfolding-prone proteins involved in neurodegenerative diseases or post-translationally modified proteins. The intrabody technology, which combines the molecular richness and selectivity of antibodies with the subtleties and power offered by gene transfer and precise subcellular targeting, shows a great potential for target validation in AD and other neurodegenerative diseases and promises to become a main weapon in the quest to find new treatments for these devastating diseases.

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PATHOLOGY OF TAU PROTEIN IN ALZHEIMER'S DISEASE

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The progression of tau pathology through different brain regions resembles in some aspects the progression found in Alzheimer disease. Tau pathology starts in the hippocampal region and afterwards it spreads to the cortex. During that process tau itself, in extracellular form, appears to be the agent that propagates the degeneration from neuron to neuron. In this review we will mainly comment on the possible mechanisms for the development of tau pathology in the brain of Alzheimer disease patients. Two major mechanisms have been proposed for the transmission of tau protein from a neuron to neuron. One of these mechanisms suggests that upon neuron death, taking place in Alzheimer disease, the released tau could be toxic for the surrounding neurons. The other one suggests a prion-like transmission, where intracellular aggregated tau is released through membrane vesicles that could be further incorporated into the surrounding neurons by endocytosis.

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MITOCHONDRIAL BIOGENESIS IN THE ISCHEMIC BRAIN: A NOVEL TARGET FOR NEUROPROTECTION

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Ischemic stroke is a serious public health problem. Despite many efforts have been devoted in preclinical research with successful results, no neuroprotective treatment has been translated from bench to bedside so far. Enhancement of endogenous brain neuroprotective mechanisms is regarded as a major research possibility at this crossroad, and mitochondria are emerging among the key regulators of these phenomena. In particular, regulatory processes of mitochondrial biogenesis take part to the adaptive responses that occur after preconditioning hypoxic-ischemic stimuli or transient global ischemia in rodent models. This could possibly contribute to neuroprotection or to augment brain tolerance to further ischemic episodes. However, in the case of severe focal brain ischemia there is evidence for a lack of adaptive mitochondrial biogenesis. Strategies to implement mitochondrial biogenesis are currently investigated as possible novel therapies directed at neuroprotection and/or neurorepair in cerebral ischemia.

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NEURODEGENERATION ABIDES BY THE LAWS OF MITOCHONDRIAL BIOLOGY

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Tuned mitochondrial physiology is fundamental for qualitative cellular function. This is true for every cell but it is particularly important for those with delicate bio-energetic equilibrium such as neurons whose pathology is frequently associated with mitochondrial dysfunction. Defects in mitochondria are key features in most neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's diseases (PD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS). When mitochondrial coupling impairs, so does cellular metabolism, trafficking of mitochondria and the cell signalling depending on this. Moreover, the quality control of mitochondria –mitophagy– results biased in neurodegeneration. In this short review, our aim is to highlight the most notable and acknowledged deficiencies of mitochondrial function and their relationship with diseases of the neurons and neuronal transmission. We shall discuss the physiological aspects of mitochondrial biology in relation to: i) bio-energy, ii) handling of the mitochondrial driven ATP consumption; iii) dynamics and iv) quality control. This with the finality to form a comprehensive picture of mitochondrial contribution to the pathophysiology of neurodegenerative conditions and conceive strategies to better diagnose and tackle these highly debilitating diseases.

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INTERLEUKIN-1 β IN CENTRAL NERVOUS SYSTEM INJURY AND REPAIR

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Acute inflammation is a self-limiting, complex biological response mounted to combat pathogen invasion, to protect against tissue damage, and to promote tissue repair should it occur. However, unabated inflammation can be deleterious and contribute to injury and pathology. Interleukin-1 β (IL-1 β), a prototypical “pro-inflammatory” cytokine, is essential to cellular defense and tissue repair in nearly all tissues. With respect to brain, however, studies suggest that IL-1 β has pleiotrophic effects. It acts as a neuromodulator in the healthy central nervous system (CNS), has been implicated in the pathogenic processes associated with a number of CNS maladies, but may also provide protection to the injured CNS. Here, we will review the physiological and pathophysiological functions of IL-1 β in the central nervous system with regard to synaptic plasticity. With respect to disease, emphasis will be placed on stroke, epilepsy, Parkinson’s disease and Alzheimer’s disease where the ultimate injurious or reparative effects of IL-1 β appear to depend on time, concentration and environmental milieu.

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ENDOPLASMIC RETICULUM STRESS IN NEURODEGENERATIVE DISEASES: THE ROLE OF RETICULON PROTEINS

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Endoplasmic reticulum stress is characterized by misfolded protein accumulation into the ER lumen, and elicits the activation of molecular mechanisms by which the cell attempts to resolve the stressful condition. However, the failure of this defensive strategy leads the cell towards ER stress-mediated cell death. ER stress has been associated to several pathological conditions among which neurodegenerative diseases, characterized by the common feature of dysfunctional protein aggregates in neuronal cells. Although ER stress occurs in these disorders, its real role in their pathogenesis still remains unclear. ER impairment could have a direct implication in the onset of the neurodegenerative diseases or maybe be a result of other trigger factors. More recently, reticulon proteins, other factors involved in ER stress induction, have been associated to several neurodegenerative disorders such as amyotrophic lateral sclerosis or Alzheimer's disease. Together these indications enforce the linkage between neurodegenerative processes and ER stress.

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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) AND BIOLOGICALS

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Progressive multifocal leukoencephalopathy (PML), is a rare, frequently fatal demyelinating disease caused by the JC virus. It is observed in severely immunosuppressed individuals with HIV infection, lymphoid malignancies and patients with organ- and stem cell transplantations. More recently, PML has been increasingly diagnosed in patients treated with biological therapies like natalizumab, efalizumab or rituximab. Informed clinical decision making as well as effective risk mitigation of medicinal products require understanding the risk of PML associated with these therapies. The main purpose of the article is to review the scientific knowledge concerning PML associated with medicinal products, in particular monoclonal antibodies.

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HSV-1 AND CNS: THE LONG TERM EFFECTS OF A LASTING AFFAIR

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Starting from the pioneering studies showing evidence of herpes simplex virus type-1 (HSV-1) genome in Alzheimer's disease (AD) brains, different epidemiological and experimental reports have proposed a possible connection between AD risk and HSV-1 recurrent infections. The main hypothesis is that, beyond massive HSV-1 entry in the brain, resulting in rare, but severe form of herpetic encephalitis, milder cerebral infection may also occur, followed by latency and virus reactivations, whose damages, may accumulate over life and result in pathologic outcomes in the elderly. This paper provides a review of literature supporting HSV-1 as a risk factor for neurodegeneration and showing the possible mechanisms involved.

SYNAPSE DISEASES AND INTELLECTUAL DISABILITY SYNDROMESC. VERPELLI¹, C. MONTANI¹, C. HEISE¹ AND C. SALA^{1,2}

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Over the last twenty years, numerous mutated genes that code for proteins concerned with synapse function have been identified in patients affected by intellectual disability syndromes. These genes may be functionally involved in synapse formation, the regulation of dendritic spine morphology, the regulation of the synaptic cytoskeleton or the synthesis and degradation of specific synapse proteins. These studies have clearly shown that even mild alterations in synapse morphology and function give rise to mild or severe intellectual disabilities. Interestingly, pharmacological agents that are able to counteract these morphological and functional synaptic anomalies can also improve the symptoms of some of these conditions. This review summarizes recent findings on the functions of some of the genes responsible for intellectual disability syndromes associated with synapse dysfunctions.