

INTRODUCTION

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EMERGING ROLE OF MITOCHONDRIA DYSFUNCTION IN THE ONSET OF NEURODEGENERATIVE DISEASES

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Mitochondria play a pivotal role in a number of biochemical processes in the neuron including energy metabolism and ATP production, intracellular Ca²⁺ homeostasis and cell signalling which are all implicated in the regulation of neuronal excitability. For this reason, it is not surprising that alterations in mitochondrial function have emerged as a hallmark of aging and various age-related neurodegenerative diseases in which a progressive functional decline of mitochondria has been described. The evidence that mitochondria are concentrated in synapses, together with the observation that synaptic dysfunction identifies an early forerunner of a later neurodegeneration, strongly suggests that significant alterations to synaptic mitochondrial localization, number, morphology, or function can be detrimental to synaptic transmission and might characterize the early stages of many neurological diseases. Thus, the characterization of both molecular players and pathway involved in mitochondria dysfunction will provide new chances to identify pharmacological target for new mitochondria-based drugs aimed at interrupting or slowing down pathological processes and/or ameliorating symptoms of neurological disorders. In this review we provide a current view on the role of mitochondria for neuronal function and how mitochondrial functions impinge on neurological diseases.

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NITRIC OXIDE AND SPHINGOLIPIDS CONTROL APOPTOSIS AND AUTOPHAGY WITH A SIGNIFICANT IMPACT ON ALZHEIMER'S DISEASE

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Aberrant regulation of signalling pathways promoting and regulating apoptosis and autophagy contributes to the development of most human neurodegenerative diseases characterised by progressive dysfunction and death of neuronal and glial cells. Both in central and peripheral nervous systems cell death is either apoptotic or autophagic, depending on the cellular setting and the initial pathogenic cue. While some mixed phenotypes have been reported, apoptosis and autophagy tend to develop into mutually exclusive ways to such an extent that they inhibit each other. The sphingolipid ceramide is a key intracellular signalling molecule involved in many cellular processes leading to either survival or death; in most of these processes also the short-lived gaseous messenger nitric oxide (NO) plays a crucial role. The crosstalk between these two messengers and their downstream mediators has been thus extensively investigated and we now have a deep understanding of it and of its multiple feedback controls. What we provide here are details on how NO- and sphingolipid-dependent signalling and their crosstalk impact on degenerative brain diseases, in particular Alzheimer's disease; we also describe how the ability of these molecules to regulate autophagy and apoptosis plays a significant role in determining the pathogenic evolution of these diseases. The evidence reported in this review suggests that targeting the NO and sphingolipid-dependent signalling pathways is worth exploiting in therapeutic perspective. In order to pursue these strategies, however, we still need to understand conclusively how the crosstalk between the NO and ceramide/sphingolipid pathways balances towards beneficial vs. toxic effects. In view of the nature of the signalling pathways involved and their multiple roles, the type of crosstalk involved is complex and intermingled with other signalling pathways.

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CHOLESTEROL METABOLISM-ASSOCIATED MOLECULES IN LATE ONSET ALZHEIMER DISEASE

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Alzheimer's disease (AD) is the most common cause of dementia and, with an aging population, poses a huge public health problem. Although a small per cent is caused by single gene changes, most AD is sporadic and unexplained. Of many modifying factors, changes in brain cholesterol homeostasis are the best studied. We present a review of the role of altered cholesterol metabolism and hypercholesterolemia in APP processing and A β generation. We also provide an overview of the potential pharmacological modulation of cholesterol homeostasis in the brain by cholesterol-lowering agents and β -cyclodextrins.

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PHARMACOLOGICAL MODULATION OF LONG-TERM POTENTIATION IN ANIMAL MODELS OF ALZHEIMER'S DISEASE

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The discovery of long-term potentiation (LTP) of hippocampal synaptic transmission, which represents a classical model for learning and memory at the cellular level, has stimulated over the past years substantial progress in the understanding of pathogenic mechanisms underlying cognitive disorders, such as Alzheimer's disease (AD). Multiple lines of evidence indicate synaptic dysfunction not only as a core feature but also a leading cause of AD. Multiple pathways may play a significant role in the execution of synaptic dysfunction and neuronal death triggered by beta-amyloid (A β) in AD. Following intensive investigations into LTP in AD models, a variety of compounds have been found to rescue LTP impairment via numerous molecular mechanisms. Yet very few of these findings have been successfully translated into disease-modifying compounds in humans. This review recapitulates the emerging disease-modifying strategies utilized to modulate hippocampal synaptic plasticity with particular attention to approaches targeting ligand-gated ion channels, G-protein-coupled receptors (GPCRs), Receptor Tyrosine Kinases (RTKs) and epigenetic mechanisms. It is hoped that novel multi-targeted drugs capable of regulating spine plasticity might be effective to counteract the progression of AD and related cognitive syndromes.

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BIMODAL EFFECT OF D-ASPARTATE ON BRAIN AGING PROCESSES: INSIGHTS FROM ANIMAL MODELS.

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Nowadays it is widely recognized that D-amino acids are present in bacteria as well as in eukaryotes, including mammals. In particular, free D-serine and D-aspartate are found in the brain of mammals. Notably, D-aspartate occurs at substantial levels in the embryo brain to then consistently decrease at post-natal phases. Temporal regulation of D-aspartate content depends on the post-natal onset of D-aspartate oxidase expression, the only known enzyme able to catabolize this D-amino acid. Pharmacological evidence indicates that D-aspartate binds and activates NMDA receptors (NMDARs). To decipher the physiological function of D-aspartate in mammals, in the last years, genetic and pharmacological mouse models with abnormally higher levels of this D-amino acid have been generated. Overall, these animal models have pointed out a significant neuromodulatory role for D-aspartate in the regulation of NMDAR-dependent functions. Indeed, increased content of D-aspartate are able to increase hippocampal NMDAR-dependent long-term potentiation (LTP) and spatial memory of adult mice. However, if exposure to elevated levels of D-Asp lasts for the entire lifetime of mice, enhancement of synaptic plasticity turns into a dramatic worsening, thus triggering an acceleration of the NMDAR-dependent aging processes in the hippocampus. Nonetheless, administration of D-Asp to old mice can restore the physiological age-related decay of hippocampal NMDA-related LTP. Besides its effect on hippocampus-dependent processes in mouse models, different points of evidence are indicating, today, a potential role for D-Asp in neurologic and psychiatric disorders associated with aberrant signalling of NMDARs.

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ENDOCANNABINOID SIGNALING IN ALZHEIMER'S DISEASE: CURRENT KNOWLEDGE AND FUTURE DIRECTIONS

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The importance of the endocannabinoid system (ECS) in the modulation functions of the central nervous system has been extensively investigated during the last few years. In particular, accumulated evidence has implicated ECS in the pathophysiology of Alzheimer's disease (AD), that is a progressive, degenerative, and irreversible disorder characterized by the accumulation in the brain of β -amyloid fragments forming insoluble plaques, and of intracellular neurofibrillary tangles (NTFs) associated with synaptic and neuronal loss. In all the processes involved in the formation of both plaques and NFTs, the key-role played by the ECS has been documented. Here, we review current knowledge and future directions of ECS modulation both in animal models of AD and in human tissues, underlying the role of endocannabinoid signaling in the development of AD hallmarks. Overall, the available data suggest that next generation therapeutics might target distinct ECS elements, for instance CB₂ receptor or fatty acid amide hydrolase, as a promising approach to halt or at least to slow down disease progression.

THE HEME OXYGENASE/BILIVERDIN REDUCTASE SYSTEM: A POTENTIAL DRUG TARGET IN ALZHEIMER'S DISEASE.

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the progressive loss of cognitive function, the inability to perform the activities of daily living and psychiatric symptoms. The formation of toxic aggregates of amyloid- β -peptide (A β), through the activities of β - and γ - secretases, is considered as the earlier event in the pathogenesis of the disease. The deposition of both A β and the following hyperphosphorylation of tau protein, trigger an exaggerate immune-inflammatory response culminating with the production of excess reactive oxygen and nitrogen species responsible for damage on cellular nucleic acids, proteins and lipids. One of the mechanisms used by neural cells to counteract oxidative/nitrosative damage in AD is the enhancement of the cell stress response. Among the main components of the cell stress response is the heme oxygenase/biliverdin reductase (HO/BVR) axis, which catalyzes the degradation of heme which is toxic if produced in excess or under redox unbalanced conditions. However, the HO/BVR system and its by-products, carbon monoxide and bilirubin, have also been shown to be neuroprotective by activating pro-survival pathways and scavenging free radicals. Nevertheless, recent research demonstrated as both the inducible isoform of HO, known as HO-1, and BVR undergo oxidative/nitrosative/phosphorylative post-translational modifications in AD brain which alter the ability of HO-1 and BVR to activate the cell stress response. In this light, naturally occurring substances or drugs (e.g. statins) that prevent the post-translational modifications leading to a controlled up-regulation of the HO/BVR system have been proposed as potential new tools for the treatment of AD.

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INTRABODIES FOR PROTEIN INTERFERENCE IN ALZHEIMER'S DISEASEG. MELI¹, N. KRAKO^{1,2}, A. MANCA¹, A. LECCI¹, A. CATTANEO^{1,2}¹*European Brain Research Institute – “Rita Levi-Montalcini”, Roma, Italy*²*Scuola Normale Superiore, Pisa, Italy*

Several open questions call for new studies on pathogenic mechanisms leading to Alzheimer's Disease (AD), with the search for upstream drivers of the neurodegeneration cascade, such as neurotrophic deficits, early misfolding events of AD-related proteins (A β and tau) and understanding the multifactorial basis of AD pathogenesis. Since seminal immunosympathectomy experiment which represents the first example of a knock out experiment (albeit a protein knock-out), antibodies have had a long and successful history as a tool to selectively interfere with the function of proteins in cells and in organisms and antibody technologies represent a major weapon in the set of target validation techniques. Here, we describe a technology, pioneered by our group, based on recombinant antibody domains exploited as intracellular antibodies (intrabodies) whereby antibodies are used as genes, rather than as proteins. We discuss several applications and new promising developments of the intrabody approach for protein interference, especially in the field of AD research.

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POTENTIAL NEURODEGENERATIVE EFFECT OF ANABOLIC ANDROGENIC STEROID ABUSE

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Anabolic androgenic steroids (AASs) are synthetic androgen-like compounds which are abused in sport communities despite their side effects. AAS abuse has been coupled with several medical complications, such as sterility, gynecomastia, and increased risk of cardiovascular and hepatic diseases. More recently, it has been observed that non-medical use of these steroids is frequently associated with changes in mood as well as cognitive deficits. Although the nature of this association is still largely unexplored, recent animal studies have shown the neurodegenerative potential of these compounds ranging from neurotrophin unbalance to increased neuronal susceptibility to apoptotic stimuli. Hence, exposure to AASs may result in a compromised brain, more susceptible, later in life, to the onset or progression of diseases not usually linked to drug abuse, especially neurodegenerative diseases.

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NEUROAIDS: VIROLOGICAL ASPECTS OF HIV INFECTIONM.A. SURDO¹, M.F. CORTESE¹, C.F. PERNO^{1,2}, S. AQUARO³

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NeuroAIDS is one of the main complications of chronic HIV-infection. The Central Nervous System is an immunologic sanctuary for HIV and allows the persistence of the virus despite an efficient antiretroviral therapy. HIV-1 could promote the neurodegeneration through the induction of inflammation by the release of neurotoxins from infected cells. In addition, several viral proteins can directly contribute to the neuronal damages, activate cell-signaling involved in the control of cellular survival and apoptosis, favoring functional alterations in the target cells. Macrophages play a key role in the pathogenesis of NeuroAIDS, they are the main reservoirs of the infection in brain, promoting the inflammatory escalation, astrogliosis and degeneration process. This review aims to highlight the virological aspects associated with NeuroAIDS including pathogenesis, and treatment of HIV-1 in the CNS sanctuaries.

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