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Cognitive function modulation during aging: a focus on L-alpha-GPE

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Abstract. – OBJECTIVE: The objectives of this review are to explore the neuronal pathways and cellular and molecular mechanisms involved in both healthy and impaired cognitive function and to discuss the role of nootropics, in particular, those with cholinergic activity, as promising interventions to preserve and/or improve cognitive performance in patients in the symptomatic pre-dementia stage, known as mild cognitive impairment (MCI).

MATERIALS AND METHODS: Papers were retrieved by a PubMed search, using different combinations of keywords (e.g., cognitive function AND aging AND nootropics), without limitations in terms of publication date or language.

RESULTS: Nootropics modulate the activities of specific brain pathways involving neurotransmitters and neuromodulators that have distinct roles in the cognitive processes. The nootropic L-α-glyceryl-phosphoryl-ethanolamine (L-α GPE), by virtue of its action as a phospholipid (PL) precursor and acetylcholine (Ach) donor, targets neural stem cell aging, cholinergic depletion, oxidative stress and microglia activation, loss of entorhinal cortex neurons, and reduced hippocampal volume. Cognitive reserve levels may be linked to the resilience and adaptability of the brain to cope with age-related cognitive decline. L-α GPE may contribute to cognitive reserve preservation via its neuronal well-being promoting action.

CONCLUSIONS: The substantial burden of age-related cognitive decline demands effective long-term and well-tolerated interventions aimed at maximizing the span of effective functioning. The use of inappropriate medication may lower cognitive reserve, thus hastening the onset of symptomatic AD, while the use of nootropics, such as L-a GPE may contribute to cognitive reserve preservation via its neuronal well-being promoting action.

Key Words:
Mild cognitive impairment, Aging, Memory, Neuronal plasticity, Nootropics.

Introduction

Cognitive impairment (CI) is a global health issue and, as such, causes a substantial individual, economic and societal burden. In addition, CI can herald the onset of dementia, which is increasingly associated with significant morbidity and mortality[1,2]. During the aging process, there is a decline in the ability to perform cognitive tasks that require one to quickly process/transform information to make a decision, including measures of speed of processing, working memory, and executive cognitive function[1]. By investigating the factors influencing the course of cognitive aging may be useful in both prevention and treatment strategies aimed at preserving cognition into advanced age. In the last decade, the notion of successful aging and the idea of compression of morbidity – maximizing the span of effective functioning while minimizing the length of time in which individuals are functionally impaired – have been largely discussed in the medical literature. In this scenario, investigating the neuronal circuits involved in cognitive aging/decline is fundamental in prolonging cognitive, physical, and psychological well-being in older adults[3,4].

Mild cognitive impairment (MCI) occurs along a continuum from normal cognition to dementia. Classified as a mild neurocognitive disorder by the World Health Organization (WHO), it is increasingly recognized as a relevant pathological condition with an estimated prevalence of 3-19% in the elderly population[5,6]. MCI is gaining recognition as a construct in a range of neurodegenerative diseases, including Alzheimer's Disease (AD) and dementia, and its presence as a common feature in Parkinson's disease[5], and multiple sclerosis[7] is in-

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creasingly documented. MCI has been regarded as a concept in evolution as definitions of subtypes, and diagnostic criteria have been introduced and modified over time, thus reflecting the evolving recognition of MCI as an early disease state in the AD continuum as well as the phenotyping-driven patient classification based on impairments in multiple or single cognitive domains. Different diagnostic criteria and subtypes of MCI have been proposed and revised over time with the further implementation of the presence of biomarkers indicative for AD pathophysiology. A very recent and detailed overview of the evolution of MCI diagnostic criteria has been recently published[6]. One important key feature is the observation that MCI causes cognitive changes that do not affect the individuals' ability to carry out everyday activities and, importantly, does not always lead to dementia. In addition, in some individuals, MCI may even revert, as observed in population-based studies[6]. Thus, MCI as a diagnostic entity has stood the test of time and currently stands as an important treatment target[6,8]. However, there is currently no effective pharmacological intervention able to prevent or slow the course of MCI. A major research effort is currently directed towards interventions that slow the rate of cognitive decline while reducing cognitive morbidity[6].

Nootropics may serve as promising treatment options to strengthen and enhance cognitive performance across a wide range of brain pathologies by virtue of their effects on brain dopaminergic, glutamatergic/cholinergic and serotonergic systems. While research has led to the synthesis of several drugs with nootropic effects, more recently, attention has shifted to the identification of nootropics from natural sources for the prevention and management of age-related cognitive decline[2]. Among nootropics of natural origin, L-α-glyceryl-phosphoryl-ethanolamine (L-α-GPE) is a promising option to target the hallmarks of MCI, including neural stem cell aging, cholinergic depletion, oxidative stress and microglia activation, loss of entorhinal cortex neurons, and reduced hippocampal volume[9-13].

This work explores the neuronal pathways and the cellular and molecular mechanisms underpinning both healthy and impaired cognitive function during aging and discusses the potential of nootropics, particularly those with cholinergic activity, to promote neuronal well-being and preserve and/or improve cognitive performance in patients with MCI.

Selection of Evidence

Papers for consideration for the present review were retrieved by a PubMed search, using different combinations of keywords (e.g., cognitive function AND aging AND nootropics), without limitations in terms of publication date and language. Papers were selected for inclusion according to their relevance for the topic, as judged by the Authors.

Neuronal Plasticity and Cognitive Function: the Brain As a Dynamic Organ

Imaging techniques, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), and increasing research in the field of cognitive neuroscience provide a unique opportunity to explore brain function by relating functional imaging to brain cell biology, neurophysiology, and metabolism[14]. Recent advances in neuroscience led to a greater awareness of the dynamic nature of our brain in which large-scale integration among local subnetworks underlies information processing and cognitive tasks – overall, we are increasingly aware that our brain is restless even at rest[15]. Thus, it is not surprising that structural and functional dynamic changes take place in the brain across the entire lifespan (during adolescence or aging)[16,17], and in both physiological (pregnancy and lactation[18]) and pathological conditions, including depression[19] and Parkinson's disease[20]. Evidence of the connection between physical changes that occur at individual synapses and behavioral evidence of learning and memory were provided by Eric Kandel et al[21], who coined the term "neuronal plasticity" as the ability of neurons to modify the strength and efficacy of synaptic transmission through a diverse number of activity-dependent mechanisms. Being plastic, neurons can modify their molecular, structural and functional output, through changes in morphology, activation of intracellular signaling cascades, regulation of synaptic density, and neurotransmitter release (or a combination of these events) in response to specific stimuli. Interestingly, the entire neuronal network is constantly evolving as being plastic and encompassing not only single neurons but also the extracellular environment.

Neuronal plasticity is due to the physical and chemical changes that occur in our brain during learning and memory processing. There is evi-

dence that learning and memory, synaptic plasticity, and neurogenesis are inter-related phenomena. Specifically, the latter two are thought to provide a substrate for specific aspects of learning and memory function[22]. Furthermore, research is ongoing to investigate whether the cellular mechanisms of neuroplasticity mediate neuronal health, hippocampal size and ultimately cognitive function[1]. Studies[23-27] on the plastic properties of neurons, along with the data of "Brain Imaging" on the structural and functional changes in different brain areas elicited by positive and negative environmental input have allowed a greater understanding of the most important brain areas involved in the modulation of cognitive functions and unveiled association between alterations in different receptors and the various chemical neurotransmitters, including γ-aminobutyric acid (GABA), glutamate and dopamine in different neural circuits and cognitive deficits. To date, GABA transmission, within the prefrontal cortex and the hippocampus, if inhibited, can have important implications on clinically relevant cognitive functions[24] while modulation of glutamate transmission *via* inhibition of the enzyme glutamate carboxypeptidase II (GCPII) has been found to improve cognition[26]. Furthermore, the importance of dopaminergic modulation of the prefrontal cortex for proper cognitive functions is also well supported by experimental evidence from non-human primates and rodents. Alterations of the dopaminergic system are frequently reported in AD patients and are commonly linked to cognitive and non-cognitive symptoms. Overall, dopamine is a well-recognized modulator of hippocampal synaptic plasticity and its binding to dopaminergic receptors in the dorsal hippocampus is a major determinant of memory encoding[25]. However, the complex structural and molecular interconnectivity among prefrontal cortex and the main nuclei (accumbens, amygdala, hippocampus) of the limbic region indicates how it is difficult to find molecules able to selectively interact with one or more specific receptors, transporters, enzymes associated to the above-mentioned neuronal pathways.

In line with the role in cognitive functions of basal forebrain cholinergic input to the hippocampus, evidence[28] suggests the involvement of acetylcholine (Ach) receptors in various aspects of neural plasticity, including long-term potentiation (LTP), regulation of brain-derived neurotrophic factor (BDNF), and hippocampal neurogenesis – indicating novel ways of preventing age-related memory decline and perhaps slowing cognitive impairments associated with neurodegenerative disorders. Accordingly, a reduction of cholinergic transmission, due to the atrophy of basal nucleus of Meynert, seems to be one of the most important neurochemical events involved in the development of the cognitive decline associated with MCI. However, it is important to take into consideration that cholinergic neurons' loss is preceded by a functional impairment of the same neurons following the accumulation of toxic molecules, such as β-amyloid, protein τ and micro fibrillary filaments which are associated with a reduced connectivity between cholinergic neurons and those producing dopamine, glutamate, GABA and norepinephrine. Moreover, astrocytes, microglia cells and the membrane lipid composition, such as phospholipids, stand as relevant factors involved in the modulation of neuronal plasticity under both physiological and pathological conditions. Accordingly, there is mounting evidence[29] that interaction between neurons and microglia drives experience-dependent synapse remodeling in the hippocampus promoting memory consolidation; thus, microglial cells contribute, *via* their essential volume-related actions in the brain, to the maturation and plasticity of neural circuits that ultimately shape behavior[30].

Finally, lipids, as key components of synaptic membranes, may also affect synaptic plasticity by shaping the membrane and modulating the levels, compartmentalization, interactions, trafficking and signaling properties of many proteins that are essential for synaptic function[28]. Thus, membrane phospholipids (PL) and proteins may play a role in cognitive function and, as such, may be potential therapeutic targets in the management of MCI.

Role of Membrane Phospholipids and Proteins in Cognitive Function

Changes at the level of neuronal membrane and, in particular, its protein and lipid machinery that controls neuronal plasticity (and ultimately cognitive function) contribute to the clinical profile of the ageing brain. Such alterations are correlated with structural and functional changes in the neuronal membrane composition (reduced PL synthesis and modified PL/cholesterol ratio with an increase in the latter component), lower availability of chemical mediators (mainly Ach) and reduced number of receptors and activation frontal and temporal cortex cells, thus impacting cognitive functioning[12].

PLs are the most abundant brain lipids and the fact that concentrations of phosphatidylcholine (PC), phosphatidylserine (PS) and phosphatidylethanolamine (PE) varies between the white (myelinated tracks) and grey matter (cell bodies) underlies a correlation between lipid composition and brain function[32]. The characteristics of PL seem to be associated with neuronal features with increased unsaturation and chain length providing higher membrane fluidity, connectivity and neurotransmitter release. The relationship between different PLs and cognitive performance has been evidenced in preclinical and clinical studies and relevant PLs in relation to cognitive performance include PS and PC, as well as the related substances sphingomyelin, and the sialic-acid-containing gangliosides[33]. Furthermore, plasma PLs were associated with cognitive function during middle adulthood, the risk of decline in verbal fluency, and a significant reduction in the risk of developing all-cause dementia[34,35]. A ten-metabolite profile containing PCs (diacyl-PC and lyso-PC) and acylcarnitines – phospholipids that have essential structural and functional roles in the integrity and functionality of cell membranes – was found to differentiate cognitively normal participants who will progress to amnestic MCI or AD within 2-3 years, from those destined to remain cognitively normal in the near future[36]. Overall, these results suggest that plasma PL levels may be useful in the detection of MCI and dementia.

The concentration and composition PLs determine the activities of enzymes, receptors, and other proteins involved in healthy cognitive function, thus providing an optimal membrane environment for protein interactions, transmission and function. Membrane presynaptic terminals are enriched with multiple proteins, each providing a specialized contribution to neurotransmission and cognitive function. Dynamic changes in synaptic terminal number, membrane protein composition, and function contribute to cognitive development during brain growth and maturation and may mediate cognitive decline during aging[37]. Screening analyses of the presynaptic protein relationships with global cognitive function in the elderly participants of the MAP (Memory and Aging Project, a community-based study) study showed that vesicle-associated membrane protein (VAMP), complexin-I, complexin-II and the SNAP-25/syntaxin interaction were associated with cognitive functioning. Greater cortical atrophy, a dementia biomarker, was reported to be associated with lower complexin-II and lower SNAP-25/syntaxin interaction[37]. Honer et al[37] suggests that greater amounts of specific presynaptic proteins and distinct protein-protein interactions may be structural or functional components of the cognitive reserve that reduces risk of dementia with aging. Scholars[38-40] support the notion that *de novo* protein synthesis has an important function in synaptic transmission and plasticity with mRNA translation in the hippocampus being spatially controlled and dendritic protein synthesis being required for different forms of long-term synaptic plasticity. Although progress has been made in evaluating the connection between memory consolidation processes and proteostasis, information on the lifetime of neuronal proteins or the dynamics of protein trafficking is still lacking[39].

Biochemical, cellular, molecular and pathological investigations improved our understanding of how protein modification and misfolding may directly harm synapses, alter neurotransmission and ultimately impair cognitive function. The soluble small aggregates of Aβ, AβOs, are currently regarded as the main species responsible for the neuronal dysfunction seen in AD by virtue of their ability to bind specifically to neurons, notably to excitatory dendritic spines, and to induce synapse damage/loss and memory impairment by multiple mechanisms[41]. Furthermore, a series of studies utilizing synthetic, natural, and human AD-derived Aβ have indicated that soluble Aβ oligomers are both necessary and sufficient to disrupt normal learning and memory function. At the two extremes of aggregation, monomers and fibrils appear to act *in vivo* both as sources and sinks of certain metastable conformations that disrupt synaptic plasticity[42]. Tau protein has been also proposed to contribute to cognitive impairment based on the observation that MCI patients exhibiting the earliest detectable clinical symptoms of dementia show accumulation of abnormally phosphorylated τ protein in CSF[43]. In line with this point, researches in a mouse model of inducible tauopathy have shown that the cognitive impairments appear to be a result of progressive neuronal loss, as well as synaptic dysfunction, depending on the levels of phosphorylated τ expression[44].

A better understanding of the mechanisms that lead to different protein expression patterns in the neural circuits that change as a function of age are urgently needed and may enable the development of more effective therapeutic treatments for memory loss. Technological advances have enabled high-throughput and cost-effective measurement of

plasma proteins. A proteome-wide study[45] of cognitive trajectory showed that proteins involving mitochondrial activity or synaptic function increased among individuals with cognitive stability irrespective of β-amyloid plaques or neurofibrillary tangles.

Last but not least, lipoxidation during aging can affect not only lipids but also lipids associated with protein structures thus leading to loss of function of key proteins involved in cell metabolism[46]; such detrimental effect underlines the contribution of lipid, mostly PL, to provide an optimal membrane environment to protein functions. While additional studies are needed, this finding adds further evidence to the clinical relevance of capturing molecular changes across all stages of cognitive decline as they may be used for early intervention and prevention. Furthermore, integrating information about these proteins with information on established biomarkers for dementia, such as amyloid β-42 and neurofilament light, may help in identifying the biological pathways to exploit therapeutically for age-related cognitive decline, preferably at the prodromal stage, when neuronal machinery may still be responsive[47]. To this end, it is imperative to characterize and unravel the structural and cellular pathobiological substrate of MCI and the cerebral features that underlie disease course and symptom presentation.

Unravelling the Cerebral Features In MCI

Despite advances in defining the clinical profile of MCI and the availability of consensus diagnostic criteria for MCI, its gross morphologic features are not easily identified with only a widening of sulci, such as the ventral ramus of the lateral fissure, as well as a blunting of the anterior tip of the temporal pole found in patients with amnestic MCI compared to those with no cognitive impairment[48].

MCI is characterized by subtle clinical-neuropsychological changes which are related to synaptic dysfunction and long-lasting pathological deposition of toxic proteins in the brain; however, the clinical-neuropsychological assessment has limited accuracy for the prediction of potential MCI conversion to AD. Clinicians may take advantage from diagnostic biomarkers, such as neuroimaging [i.e., MRI, F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) and amyloid-PET] and cerebrospinal fluid-CSF [i.e., Aβ42, total (t-Tau) and phosphorylated (p-Tau) Tau measures]. Of note, prodromal AD relates to only the amnestic portion of the MCI clinical criteria, and it is augmented by evidence of Aβ either from PET scanning or CSF or the presence of an abnormal tau/Aβ ratio in the CSF[8].

In patients with MCI, an initial period of increased brain activation in response to cognitive demand is followed by decreased activation as disease progression continues, eventually exhausting the compensatory response. In order for interventions targeting plasticity to be effective, the brain must still be capable of compensation for deficits that maintains functional ability or performance. Although a degree of plasticity seems to be maintained throughout the early stages of AD, the critical period for treatment maybe prior to AD diagnosis supporting the clinical benefit of an earlier intervention in MCI patients[49].

The pathophysiological signature of MCI includes molecular, neurochemical and structural alterations, synaptic degeneration, cell loss, reduction in neurotrophic function and neuronal selective vulnerability. Neuronal loss occurs in the limbic medial temporal lobe and particularly in the entorhinal cortex, while the hippocampus displays a significant decline in plasticity[48]. Thus, the limbic area appears particularly affected in MCI. Structural MRI studies and functional studies using FDG-PET and brain perfusion single-photon emission computed tomography (SPECT) have shown gray matter loss in the entorhinal and hippocampal areas and hypometabolism or hypoperfusion in the posterior cingulate cortex and precuneus at MCI stage[50,51]. Interestingly, such profile seems to predict rapid conversion to AD. Yue et al[52] have also shown that MCI patients displayed significant decreased right hippocampal and amygdala volume than controls. For asymmetry pattern, a ladder-shaped difference of left-larger-than-right asymmetry was found in amygdala with MCI > controls, and an opposite asymmetry of left-less-than-right pattern was found with controls > MCI in hippocampus. Furthermore, Wachinger et al[53] investigating the symmetries of neuroanatomical structures across subcortical and cortical brain regions have shown that the hippocampus shows a significant increase in asymmetry longitudinally and both hippocampus and amygdala display a significantly higher asymmetry cross-sectionally concurrent with disease severity above and beyond an ageing effect. Importantly, shape asymmetry in hippocampus, amygdala, caudate and cortex appears predictive of disease onset.

Hippocampal shrinkage and synapse loss occur early in the pre-symptomatic and MCI phases of AD, thus promoting earlier therapeutic interventions to remove disease triggers and stop neurodegeneration before overt memory loss[54]. Alterations in plasticity and connectivity have also been reported in MCI as disruption and loss of synaptic connectivity result in progressive cognitive decline due to white-matter abnormalities and anatomical/functional deficits[2]. A primary mechanism by which synaptic connectivity is altered may involve expression and responsiveness to neurotrophins. Within the adult hippocampus, trophic factors in BDNF, play a central role in synaptic remodeling associated with memory. Siuda et al[55] showed that lower BDNF serum levels were directly correlated with the severity of CI with significantly lower levels in AD patients compared to those with MCI and control subjects. Changes in neuronal circuits involved in cognition have been documented in MCI with cholinergic basal forebrain neurons containing early and late tau conformational markers of neurofibrillary tangles and increased activity of choline acetyltransferase in both hippocampus and superior frontal cortex[48]. From a cellular standpoint, alternations in essential metabolic processes for energy supply and PL membrane function have been implicated in the pathological process. FDG-PET studies[56] have shown glucose hypometabolism in the retrosplenial cortex (RSC) and medial temporal lobe in people with MCI while *postmortem* studies found reduced levels of the major membrane components, such as PC, PE and phosphatidylinositol. The human brain is highly vulnerable to changes in energy metabolism, due to its relatively large energy consumption. It is subject to free radical-induced lipid peroxidation (it uses one-third of the inspired oxygen), is rich in polyunsaturated fatty acid (targets for free radical attack), is high in redox transition metal ions and low in antioxidant capacity[57]. As a result, increasing evidence indicates oxidation of lipids, numerous proteins, DNA, and RNA in multiple brain regions in subjects with MCI.

To better understand the pathogenic mechanisms of MCI, appropriate models of CI are necessary. Middle-aged rats and mice, rats with brain ischemia, transgenic mice overexpressing amyloid precursor protein and presenilin 1 (tested at an early stage), or aging monkeys are promising candidates[58]. However, a major concern is how to distinguish MCI models from AD animal models as faces the physician in clinical practice of having to distinguish between MCI and the initial stages of AD. Although these animal models have been used to test drugs for the treatment of the memory deficits, a validation of the models through comparable therapeutic results in animals and humans is lacking. Much research is being carried out to identify alternative models of CI with sleep deprivation recently endorsed as a cognitive challenge model of CI arising in AD by virtue of both partially overlapping spectrum of induced cognitive deficits and their response to pharmacological treatment[59].

Therapeutic Targets in MCI: Exploiting Cortex and Hippocampus Cell Types and Functions

To date, research in cognitive impairment and AD has been neuron-oriented but Nirzhor et al[60] suggest that glial cells are linked to AD pathogenesis and may offer potential therapeutic targets against AD by virtue of their role in preserving the structural integrity of neurons and maintaining homeostasis (i.e., concentration of ions, neurotransmitters, etc.) within the CNS. Increases in microglial activation in the prodromal stage of AD have been reported, including in inferior and medial temporal regions where early neurodegenerative changes occur. Furthermore, in MCI patients a relationship between microglial activation and fibrillary amyloid deposition in cortical regions that typically have high plaque load in AD was observed providing additional evidence for the microglia as potential cellular targets in MCI[61].

Neuronal 'well-being' also relies on the neural stem cells (NSCs) – a subpopulation of cells in the dentate gyrus of the hippocampus and in the subventricular zone of the lateral ventricles capable of self-renewal and differentiation (adult neurogenesis). Adult neurogenesis is related to the amelioration of impaired neurons and CI. Although neurogenesis continues throughout life, it decreases with age due to an intrinsic decline in NSC responsiveness[10]. Furthermore, in aged NSCs, changes in the amount and composition of membrane proteins/lipids have been reported leading to a reduction in membrane fluidity and cholinergic activities. As a result, molecules that are effective at normalizing membrane composition and cholinergic signaling may counteract stem cell aging[10].

The secretome of human NSCs plays a pivotal role in promoting neuroprotection and regeneration. Factors produced by NSCs provide an environment that allows injured cells to resist further degeneration, promote repair, drive regeneration of injured tissue, and decrease inflammation[62]. BDNF secreted from NSCs is essential in rescuing cognitive function in AD. The beneficial effects of NSCs on cognition are not mediated by alteration of Aβ or tau pathology, instead, NSC-derived cells increase hippocampal BDNF leading to improved synaptic density and restoration of hippocampal-dependent cognition[63]. Cell function can also be used as a target in MCI management. Mitochondria regulate the functions of healthy neurons that are highly dependent on oxidative phosphorylation to meet energy demands and are particularly susceptible to energy hypometabolism. Neurons are non-dividing cells and are not replaced during life, with the exception of the hippocampus that continuously generates new neurons during adulthood. This means that neurons accumulate oxidative stress and defective mitochondria during aging[64] and at the early stages of AD[65] have been documented. The mitochondrial cascade hypothesis identifies mitochondrial dysfunction as a central pathologic mechanism in age-related degenerative disorders and indicates mitochondria as promising targets for therapeutic strategies. Pharmacological studies on improving mitochondrial function, such as ATP production and respiration or in reducing mitochondrial harmful by-products, such as radical oxygen species, (ROS) are indicated[5]. MCI is neuropathologically complex and cannot be defined within a single framework. Determining which factors primarily drive neurodegeneration and dementia and which are secondary features of disease progression requires further research. Nevertheless, available evidence indicates potential therapeutic avenues that are worth pursuing, such as the nootropics that modulate the activities of specific brain pathways involving neurotransmitters and neuromodulators that have distinct roles in the cognitive processes[2].

MCI Clinical Management: Role of Nootropics

The goals of MCI management are to improve memory loss and prevent further cognitive decline. Early interventions and treatments should improve cognitive performance while delaying or preventing further progressive deficits. Given the well-documented pathophysiological relationship between MCI and AD, therapeutic interventions for MCI are based on treatment strategies for AD including acetylcholinesterase inhibitors (AChEIs), antioxidants, nootropics, and anti-inflammatory drugs. Nootropics have been available for over three decades and are the agents most frequently indicated for the initial treatment of dementia-related symptoms and age related cognitive impairment[66]. Also known as 'smart drugs', nootropics are thought to enhance cognitive parameters, such as memory, creativity, motivation, attention and more in general the executive processes[2]. Multiple mechanisms of action have been proposed for the beneficial effects of nootropics on memory and learning, including blockage of calcium channels, inhibition of AChE activities, increase in the level of antioxidants and in synaptic and mitochondrial response genes.

Kell et al[67] suggested that therapeutically relevant *in vitro* and *in vivo* concentrations of piracetam, the prototype of the so-called 'nootropic' drugs, are able to improve mitochondrial dysfunction associated with oxidative stress and/or aging. Mitochondrial stabilization and protection might be an important mechanism to explain many of piracetam's beneficial effects in elderly patients. Gray et al[68] have shown *in vivo* that *Centella Asiatica*, a nootropic of natural origin, modulates antioxidant and mitochondrial pathways. Daniele et al[10] in human stem cells have shown that L-α-glyceryl-phosphoryl-ethanolamine (L-αGPE) cell treatment significantly protected the redox state and functional integrity of mitochondria, and counteracted senescence and NF-κB activation.

Nootropics may also have neuroprotective effects reducing Aβ accumulation, synaptic dysfunctions, inflammation, apoptosis, and oxidative stress[69]. Nootropics have been demonstrated to protect against experimentally induced disruption of acquisition, retention or retrieval in animal models in either passive avoidance or similar procedures[70]. Advantages of the nootropics include absence of adverse effects usually associated with neuropsychotropic drugs, good long-term tolerability and adherence to therapy. They improve cognitive functions[70] and have documented long-term efficacy in a variety of conditions involving decreased mental acuity from mild to moderate.

The cholinergic system plays an important role in the regulation of synaptic communication and plasticity in the hippocampus and the firing of cholinergic inputs into the hippocampus

from the medial septum seems to be important in learning and memory[71]. Given the role played by Ach in learning and memory, the effectiveness of nootropics with a cholinergic activity is well documented[72]. Compounds that induce a sustained activation of postsynaptic Ach receptors, such as lecithin, citicoline, acetylcarnitine and choline alfoscerate are mainly used in the treatment of cognitive deficits with a vascular and degenerative origin. However, increasing Ach availability with only precursor administration may not always be correlated with improved cognitive functioning. This is in contrast to what observed in PD in which improving dopamine availability *via* its precursor L-Dopa causes an immediate functional improvement. In MCI restoring Ach bioavailability seems not to be sufficient. One reason may be that Ach exerts cellular, genomic and functional activities thereby promoting a virtuous circuit improving neuronal well-being. It has therefore been suggested that rather than just providing a substrate, it is necessary to also ensure that the neuronal environment is 'plastic' and responsive to allow Ach to contribute to neuronal well-being.

To this end, it can be hypothesized that, along with Ach availability, the normalization of PL content at the neuronal membrane level is critical as it may contribute to neuronal plasticity and in general to an efficient neuronal ecosystem where preservation of PL pool is crucial not only for membrane fluidity but also for PL biosignalling function. Modulation of membrane PL content influences organelles and protein function; furthermore, the lipid composition of membranes may also influence the processing pathways of the transmembrane protein APP or the formation of toxic oligomeric Aβ[73-75]. Among nootropic compounds, citicoline potentiates neuroplasticity and is a natural precursor of phospholipid synthesis, chiefly phosphatidylcholine, and was hypothesized to protect cell membranes by accelerating resynthesis of phospholipids, thus resulting in rapid repair of injured cell surface and mitochondrial membranes[76]. Whether the supplemented choline restored deficits of particular lipid metabolites in the cellular lipid pool, or if it boosted the levels of key metabolites that may have greater bioactivity is less clear[74]. Among nootropics, L-α-glyceryl-phosphoryl- ethanolamine (L-α GPE), known to improve cognitive impairment in neurodegenerative diseases, is unique and is involved in the biosynthesis of the cellular membrane PL as a direct substrate for the synthesis of PE and then PC[11].

L-α GPE: Preclinical and Clinical Evidence In MCI

L-α GPE improves the neuronal structures involved in learning and memory by two mechanisms: as a precursor of PC and as a direct source of the major components of the phospholipid bilayer, PE and PC[11]. Accordingly, the latter has been shown to contribute to recover astrocytes from the general redox derangement induced by different amyloid fragments and possibly to protect from inflammation, gliosis and neurodegeneration[11]. Restoring the membrane stores of PL is promising in counteracting NSC aging as evidence suggests that replenishing the NSC membrane composition by PC supplementation improves hippocampal neurogenesis while reducing soluble tumor necrosis factor-alpha (TNF-α) levels and ultimately counteracting systemic inflammation. Furthermore, the glycerophospholipid PS has been shown to improve NSC function and cholinergic transmission, leading ultimately to improvement of memory and learning[10]. These observations provided the rationale to investigate if administration of L-α GPE counteracts NSCs senescence. Daniele et al[10] demonstrated that L-α GPE improved proliferative potential of cells and mitochondrial metabolism, decreased ROS production, and blocked the inflammatory pathway by reducing NF-kB activation – properties that may be in part associated with its ability to act as a PC precursor and an Ach donor[10]. In human hippocampal neurons, L-α GPE increased phospholipids (PC and PE) and Ach, leading to improved membrane function by reducing lipid peroxidation and enhancing membrane fluidity, as well as inducing autophagy and exerting cytoprotective effects in aged cells. Overall, these results show the beneficial effects of L-α GPE supplementation and support its use as a potential therapeutic agent to preserve hippocampal neurons and memory performance[9].

L-α GPE demonstrated a significant improvement in behavioral performance in *in vivo* models of cognitive impairment, such as the active avoidance-conditioning test[77]. Furthermore, sub-chronic administration enhanced receptor-mediated neuronal signal transduction (cAMP and IP production), possibly by increasing coupling between neurotransmitter receptors and their intracellular effectors through improved neuronal membrane fluidity. It has been suggested that these neurochemical modifications may explain at least in part, the molecular mechanisms of L-α GPE at the brain level. These preclinical observations

provided further evidence for the use of L-α GPE in humans to maintain brain function during the aging process, and the scientific rationale for investigation in patients with mild age-related cognitive disturbances[77]. In an early clinical study in patients with senile psycho-organic syndrome treatment with L-α GPE resulted in a significant symptoms' reduction and improved learning and memory functions compared to placebo, as well as significant reductions in depressed mood, insomnia and cenesthopathy[12]. A subsequent pilot double-blind, randomized, parallel group multicenter study was carried out in patients with mild to moderate AD to compare efficacy and safety of L-α GPE with donepezil. Although no significant differences were reported in clinical parameters such as the Gottries-Brain-Steen Scale (GBS), Questionnaire for Memory Disorders (QDM) and Clinical Global Impression (CGI), greater clinical improvement in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) score was observed in L-α GPE treated patients[13]. While these observations are promising, further clinical studies are urgently awaited to determine the therapeutic role of L-α GPE in a range of cognitive impairment-associated neurological conditions.

The rationale for use of L-α GPE is based on its neuroprotective properties as a result of its ability to provide both precursors of the main membrane PL, thus preserving membrane fluidity, and of Ach by restoring neuronal transmission, as well as its action on the neural stem cells pool and microglia, which both contribute to improve neuronal plasticity and function. Furthermore, given the potentiality of antidepressant drugs to stimulate both NSCs proliferation and the expression of BDNF in the hippocampus, L-α GPE could be used in synergy with antidepressants to potentiate cognitive processes.

Future Perspectives

The world's population is ageing with implications for all sectors of our society. Interventions aimed at decreasing the social and financial costs of declining cognitive function are increasingly being investigated. Characterization of the cellular and molecular mechanisms involved in CI during aging and its progression to frank neurodegenerative diseases is vital to understand the aging process. Despite major advances in neuroscience that have enabled us to gain an in-depth knowledge of the role of synaptic plasticity in learning and memory function, we are still missing many pieces of the puzzle and we only partially appreciate the complexity behind the transition from normal ageing to CI. There are many hurdles to overcome before we can effectively manage MCI and successfully implement interventions targeting morbidity compression and preservation of cognitive reserve.

Diagnosis of MCI is problematic since patients who report having cognitive problems may have normal scores on global cognitive scales or in brief neuropsychological instruments. In addition, the variability in clinical practices across centers demands better biomarker counseling and training to improve communication skills. Future initiatives should address the importance of communicating preventive strategies and advance planning. It is critical to assess instrumental activities of daily living (iADL) that reflect complex activities in the evaluation of individuals with MCI as their impairment, combined with changes in cognitive markers, indicates a higher risk of progression to dementia[78]. As advocated by Kasper et al[6], it is vital to update existing guidelines based on available evidence and to disseminate consensus diagnostic criteria for MCI when available, as well as working towards an early recognition and accurate classification of MCI subtypes. Such approach may help us to improve management of MCI and recognize the importance of this disease stage within the AD continuum which is important as mixed pathologies are common in MCI and a multi-targeted treatment approach should be pursued. Finally, to define a profile characterizing the state of MCI, we may take advantage from brain tissue banks that use standardized MCI criteria, neuropathological protocols including staining and scoring techniques[79].

Identifying biological correlates of late life cognitive function is important if we are to ascertain biomarkers and to develop treatments to help reduce age-related CI. Future studies should focus on which lipids change with age in different areas of the brain areas and how they relate both to the function of the area and to the dysfunction leading to neuropathology. The available evidence is on qualitative alterations in lipid composition, however, quantitative lipidomic analyses may contribute to accurately define changes[80]. As the composition of neuronal proteins ultimately dictates synaptic function, it might be effective for future studies to focus on determining how biological correlates of aging affect the synthesis and activity of proteins known to have roles in long-lasting forms of synaptic plasticity and memory.

Available evidence indicates a series of potential therapeutic avenues worth pursuing including the nootropics, able to modulate the activities of specific brain pathways involving neurotransmitters and neuromodulators that have distinct roles in the cognitive processes. The nootropic L-α GPE, by virtue of its action as a PL precursor and Ach donor, holds great promise as an effective option to target the hallmarks of MCI including neural stem cell aging, cholinergic depletion, oxidative stress and microglia activation, loss of entorhinal cortex neurons and reduced hippocampal volume[9-13]. However, despite its widespread use in clinical practice, published evidence from clinical trials is limited[12,13] and further studies to support its promising potential in MCI management are required. Nevertheless, it appears preferable to other commonly used nutritional approaches, including flavonoids, some vitamins and other natural substances that are claimed to be beneficial for the maintenance of a good cognitive performance[81]. Compared to nutraceuticals which display a late onset of action, L-α GPE is rapidly absorbed at a gastrointestinal level and when administered in animal models a rapid uptake from systemic tissues including brain has been observed[82]. The course of AD implies a preclinical stage whose duration in part depends on the rate of pathologic progression, which is offset by compensatory mechanisms, referred to as cognitive reserve. Cognitive reserve levels may be linked to the resilience and adaptability of the brain to cope with age-related cognitive decline. The use of inappropriate medication may lower cognitive reserve thus hastening the onset of symptomatic AD[83], while the use of nootropics, such as L-α GPE may contribute to cognitive reserve preservation *via* its neuronal well-being promoting action.

Conclusions

By integrating three different perspectives namely biology, pharmacology and clinical practice, our work explores how contributions stemming from neuronal pathways and cellular mechanisms may impact MCI onset, progression to AD and its therapeutic management. Along with a review of the latest available evidence on the cellular and molecular mechanisms underpinning both healthy and impaired cognitive function during aging, we focus our attention on how this knowledge can be applied to better address disease course and management objectives. Overall, the substantial burden of age-related cognitive decline demands effective long-term and well-tolerated interventions aimed at maximizing the span of effective functioning. The use of inappropriate medication may lower cognitive reserve thus hastening the onset of symptomatic AD, while the use of nootropics such as L-α GPE may contribute to cognitive reserve preservation via its neuronal well-being promoting action.

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Authors' Contributions

All authors contributed equally to this work. All authors take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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