Neurochemistry International 126 (2019) 195–202

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

# Can magnesium reduce central neurodegeneration in Alzheimer's disease? Basic evidences and research needs

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ARTICLE INFO

*Keywords:*
Magnesium
Alzheimer's disease
NMDA
β-Amyloid
Neurodegeneration

ABSTRACT

Magnesium (Mg) is a crucial divalent cation with more than 300 cellular functions. This ion shows therapeutic properties in several neurological diseases. Although there are numerous basic evidences showing that Mg can inhibit pathological processes involved in neuroglial degeneration, this low-cost option is not well-considered in clinical research and practice for now. Nevertheless, none of the expensive drugs currently recommended by the classic guidelines (in addition to physiological rehabilitation) had shown exceptional effectiveness. Herein, focusing on Alzheimer's disease (AD), we analyze the therapeutic pathways that support the use of Mg for neurogenesis and neuroprotection. According to experimental findings reviewed, Mg shows interesting abilities to facilitate toxin clearance, reduce neuroinflammation, inhibit the pathologic processing of amyloid protein precursor (APP) as well as the abnormal tau protein phosphorylation, and to reverse the deregulation of N-methyl-D-aspartate receptors. Currently, some crucial details of the mechanisms involved in these proved effects remain elusive and clinical background is poor. Therefore, further studies are required to enable a better overview on pharmacodynamic targets of Mg and thus, to find optimal pharmacologic strategies for clinical use of this ion.

## 1. Introduction

Magnesium (Mg) is, by its abundance, the second intracellular cation and the fourth cation of the human body (Allgrove, 2009). This ion has a major role in more than 300 cytosolic enzymatic reactions (mitochondrial energy production, protein synthesis, survival signaling, proteins' spatial configuration, regulation of nucleic acids' activity, etc.) (Allgrove, 2009; de Baaij, 2015). Due to its multiple functions and properties, Mg is considered for therapeutic use in several diseases, particularly neurological pathologies with excessive apoptosis or dysexcitability (Kirkland et al., 2018). Moreover, for the clinician, Mg offers a low-cost treatment option with a large therapeutic window. However, the use of this ion is not well codified for most of the pathologies it can be used for. Indeed, although there are numerous basic evidences of the effectiveness of Mg in some neuropathological processes, there are not enough translational and clinical studies for guidelines editing. Thus, Mg use is not widely considered by clinical teams even though it could be effective as adjuvant to classic therapy. Currently, in neurodegenerative diseases, palliative medical/surgical therapies (usually expensive drugs or deep neurostimulation) and rehabilitation (kinesitherapy and cognitive training) are required to delay as much as possible the fatal evolution (Bond et al., 2012; Pouryamout et al., 2012). Herein, we present and demonstrate that Mg should be more considered in the management of neurodegenerative diseases, focusing on the example of Alzheimer's disease (AD). Therefore, based on its relevant biological properties, we presented the pharmacodynamic targets expected in the use of this ion for AD.

## 2. Overview on AD

AD is the most frequent (60–70% of dementia cases) and well-studied neurodegenerative disease (Burns and Iliffe, 2009). It is an early progressive dementia characterized by diffuse brain atrophy (mainly temporal lobe, parietal lobe, cingulate gyrus and anterior lateral frontal cortex), extracellular plaques of aggregated beta-amyloid (Aβ) and intraneuronal neurofibrillary tangles (NFTs) (Burns and Iliffe, 2009). Plaques are insoluble deposits resulting from the accumulation of Aβ′s polymers, combinations of small peptides of 39–43 amino acids

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https://doi.org/10.1016/j.neuint.2019.03.014
Received 5 December 2018; Received in revised form 15 January 2019; Accepted 18 March 2019
Available online 22 March 2019
0197-0186/ 

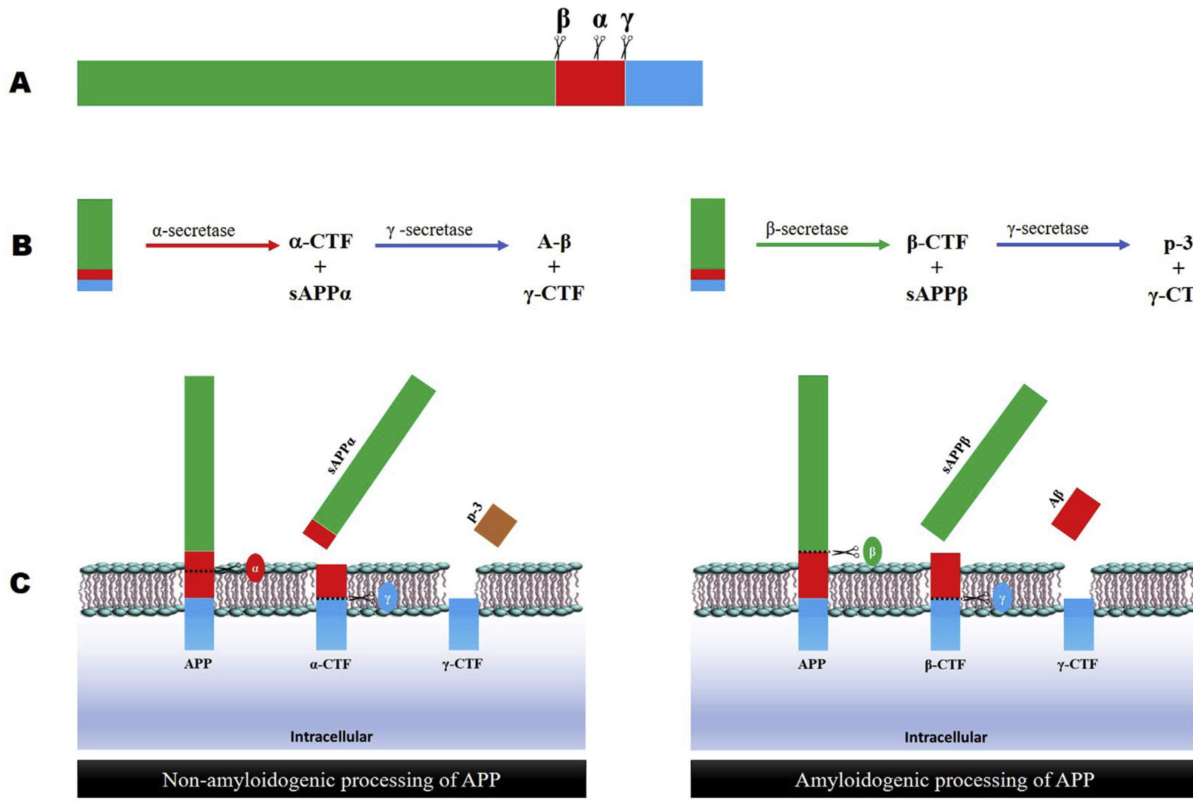


**Fig. 1. Amyloid precursor protein (APP) processing.**|
***A)*** Cleavage sites of APP by α- β- and γ-secretase. ***B - C)*** α-versus β-processing of APP: α-secretase cleaves APP within the Aβ protein domain, resulting in soluble APP-α (sAPPα) release, whereas β-secretase's action releases sAPPβ. For both processing, residual chains (C-terminal fragments or CTF) remain bound to membrane: CTFα in α-processing and CTFβ in β-processing. Then, γ-secretase release extracellular P3 from CTFα and Aβ protein from CTFβ.

synthetized by the fragmentation of a larger protein (Fig. 1): the full-length amyloid precursor protein (APP) (Burns and Iliffe, 2009; Chen et al., 2017). APP is a transmembrane protein that is crucial for neuronal plasticity and survival. This protein is composed of a large extracellular domain, a short transmembrane domain, and a cytoplasmic tail (Chen et al., 2017). APP processing depends on three proteases located at distinct intracellular zones: alpha-secretase (α-secretase) that is anchored in the cell membrane, whereas beta- and gamma-secretase (β-secretase and γ-secretase) are within endocytic compartments (Chen et al., 2017; Seegar et al., 2017). The proteolytic reaction that produces Aβ is catalyzed by two proteases: the β-secretase and then the γ-secretase (Chen et al., 2017). It is important to notice that although plaques of Aβ are the main neuropathologic hallmarks of AD, several studies revealed that soluble aggregates of Aβ are earlier involved in the pathogenesis and are likely to be more correlated to the clinical severity (Cline et al., 2018). These soluble aggregates are oligomers of Aβ (oAβ) and two types are well-studied in AD's neuroglial impairing: amyloid-β dimers and Aβ*56 (Amar et al., 2017; Klyubin et al., 2008; Lesné et al., 2013; Shankar et al., 2008). The other pathogenic phenomenon in AD, NFTs, is due to abnormal aggregation of the tau protein. In physiological conditions, this molecule, when phosphorylated, stabilizes the microtubules and thus, is crucial for cell transport. In AD, an hyper-phosphorylation of tau (mainly involving oAβ′s toxicity) causes cross-pairing and results in tangles constitution with alteration of neuronal transport system (Amar et al., 2017; Lesné et al., 2013; Sherman et al., 2016). The ultimate consequences of these pathologic processes are regional loss of brain connectivity and neurons' death.

## 3. Physiology of Mg

The plasmatic level of Mg (0.75–1.4 mmol/L) is finely balanced, in response to variable absorption, by changes in urinary excretion (de Baaij, 2015). In the plasma, magnesium exists mainly in free ionized form (55%) (Sztark and Cochard, 1998). About 34% is bound to proteins with the remaining 11% forming complexes with molecules such as phosphates and citrates (Sztark and Cochard, 1998). Regarding the intracellular pool, less than 10% is present in free ionized form (Sztark and Cochard, 1998).

Mg influences the metabolism of excitable cells as well as their transmembrane and intracellular ion transfers (Allgrove, 2009). These functions give it a key role in membrane electrical stability, neuroglial communication, and thus neuroglial viability (Trapani et al., 2011). Furthermore, intracellular free Mg and Mg-ATP complex act in a coordinate control of protein synthesis and cell proliferation (Rubin, 2011). The Mg ion is also involved in neurotransmission, mainly N-methyl-D-aspartate (NMDA) glutamatergic transmission (Spasov et al., 2009). In this activity, Mg regulates postsynaptic activation by modulating the sensitivity of NMDA receptor channel to glutamate (Nikolaev et al., 2012). This ion is also involved in the control of extrasynaptic NMDA receptors (Nikolaev et al., 2012). Apart from its postsynaptic activity, Mg also modulates the probability of glutamate presynaptic releasing and the releasing/uptake of this neurotransmitter by astrocytes (Furukawa et al., 2009; Kirkland et al., 2018). Overall, Mg is involved in cellular pathways related to cell survival as well as cell death, depending on its intracellular availability (Trapani et al., 2011; Wolf and Trapani, 2008). This double role implies that intracellular Mg can activate either survival cascade or apoptosis cascade, depending of its cytoplasmic level (Wolf and Trapani, 2008).

## 4. Main clinical and experimental observations linking Mg's level and neurodegeneration

Several studies in humans and in animal models showed that low or high levels of Mg can lead to neurodegenerative disease (Kieboom et al., 2017; Kirkland et al., 2018), epilepsy (Arjona et al., 2014; Gandhi et al., 2012), headaches (Lodi et al., 2001) and other neurological disorders. Moreover, Mg's supplementation demonstrates therapeutic properties in different pathophysiological brain conditions.

### *4.1. Magnesium's dysmetabolism in brain neurodegeneration*

Hypomagnesemia is the most involved dysmetabolism in brain degeneration. First, hypomagnesemia-induced seizures are well described in severe congenital hypomagnesemia (Chen et al., 2016). Interestingly, these seizures are usually associated with severe cognitive impairments and brain atrophy when a suitable supplementation is not early initiated (Ndiaye et al., 2013). Other clinical studies suggest the role of abnormal Mg levels in primary neurodegenerative diseases. For dementia, Kieboom et al. (2017) studied the incidence of this impairment in 9569 patients with normal cognition at baseline (median follow-up of 7.8 years). They found that low serum Mg levels ($\leq$0.79 mmol/L) as well as high levels ($\geq$0.90 mmol/L) were associated with an increased risk of dementia. In another study including 101 patients, Barbagallo et al. (2011) found that Mg-ion (but not total Mg) was significantly lower in the AD group as compared to age-matched control adults without AD (0.50 $\pm$ 0.01 mmol/L vs 0.53 $\pm$ 0.01 mmol/L; $p < 0.01$). Moreover, in a systematic review analyzing 13 studies (including 559 patients with AD, 381 healthy controls, and 126 patients with other medical illness), Veronese et al. (2016) reported lower Mg in cerebrospinal fluid (CSF) but not in serum of AD patients. For Parkinson's disease (PD), lower Mg levels in CSF were also reported whereas serum levels were not clearly reduced in PD patients versus controls (Kirkland et al., 2018). Furthermore, in animal models, Oyanagi et al. (2005, 2006) reported that continuous low Mg intake for two generations induces selective loss of dopaminergic neurons in rats. Aside from neuroglial alterations, low-levels of extracellular Mg increase the oxidative stress generated in endothelial cells by hydrogen peroxide exposure (Wolf et al., 2008). Such dysmetabolism can lead to a blood-brain barrier (BBB) dysfunction and alterations in brain microperfusion, with degenerative consequences (Burns and Ilffe, 2009; Horgusluoglu et al., 2017).

### *4.2. Magnesium supplementation against brain neurodegeneration*

Numerous studies have shown interesting therapeutic properties of Mg in neurodegeneration. However, most of these works were experimental, using *in vitro* preparations or animal models. In kainate mouse model of mesial temporal lobe epilepsy, Mg supplementation reduces the severity of spatial memory impairments (Toffa et al., 2018). In another study, Hashimoto et al. (2008) reported both preventive and ameliorating effects in an *in vitro* rat model of PD disease involving 1-methyl-4-phenylpyridinium (MPP+). To appreciate the efficacy, they evaluated dopaminergic neurons' survival and the length of dopaminergic neurites. The therapeutic effect was dose-dependent and thus, a Mg concentration of 1.2 mM significantly inhibited the toxicity of MPP + whereas a concentration of 4.0 mM completely prevented any neuronal loss.

## 5. Basic supports': magnesium against neurodegenerative processes in AD

Various pathological phenomena involved in AD are expected to be targeted by Mg.

### *5.1. Neuroinflammation*

Neuroinflammation is considered as a critical factor of neuronal loss and neuroglial dysfunction in major neurodegenerative diseases (Ilievski et al., 2018; Rakic et al., 2018; Walker et al., 2015; Wenzel et Klegeris, 2018). In AD, the inflammation is triggered by Aβ oligomers at the early stages and then, by Aβ′s deposits and toxic leakages through the blood-brain-barrier (Wenzel et Klegeris, 2018; Yamazaki et Kanekiyo, 2017). An excessive proinflammatory-cytokines releasing, particularly gamma-interferons (IFN-γ), interleukine 1-beta (IL-1β) and tumor-necrosis factor alpha (TNF-α), with subsequent consequences, is the main process involved (Ilievski et al., 2018; Rakic et al., 2018; Wenzel et Klegeris, 2018). Astrocytes and then microglia (with later blood immune cells involvement) play a major role in this inflammatory process (Chun et al., 2018; Perez-Nievas and Serrano-Pozo, 2018). Park et al. (2018) demonstrated that both gamma-interferon (IFN-γ) (released by reactive astrocytes) and excessive Aβ (from neurons) induce microglial activation respectively via IFN-γ receptors and toll like receptors 4 (TLR4). According to these authors, microglia then promote the expression of inducible nitric oxide synthase (iNOS) and nuclear factor-kappa B (NF-κB) and release TNF-α and cytotoxic NO, resulting in neuronal degeneration. Interestingly, following Mg treatment, some studies reported an *in vivo* reduction of microglial activation in rats' severe preeclampsia model (Johnson et al., 2014), and an *in vitro* calcium-related inhibition of the inflammatory response of macrophage-like cells to lipopolysaccharides exposure (Lin et al., 2010). Moreover, Mg showed an inhibitory effect on neuronal gamma-secretase and microglial TNF-α (Yu et al., 2018). For note, γ-secretase is a crucial protease complex for Aβ synthesis. Its hyperactivity leads to neuronal accumulation of this substrate and microglial TNF-α overexpression resulting in subsequent neurodegeneration. Using *in vitro* human- and *in vitro* mouse-derived cells, Yu et al. (2018) emphasized that Mg acts by decreasing γ-secretase activity in neurons as well as suppressing TNF-α expression in microglia. The authors also demonstrated that phosphoinositide-3-kinase/protein kinase B (PI3-K/Akt) and NF-κB signaling is crucial for these neuroprotective properties of Mg. An IL-1β suppression has also been found with Mg supplementation (Wang et al., 2017). Indeed, Wang et al. (2017) showed that Mg blocks IL-1β- and Aβ-induced inflammation. Moreover, they demonstrated that this suppression results from the stimulation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) and peroxisome proliferator-activated receptor gamma (PPARγ) (Wang et al., 2017).

### *5.2. APP cleavage and Tau protein metabolism*

In the neural network dysfunction of AD, Aβ and tau protein accumulation plays a critical role (Crimins et al., 2013; Kamat et al., 2016). These phenomena are partially reversible (Pooler et al., 2014). Thus, enzymatic reactions resulting in such toxic accumulations constitute interesting therapeutic targets. Some of the concerned reactions can be modulated by Mg as revealed by several experimental findings. Yu et al. (2010) evaluated the effects of varying concentrations of extracellular Mg on APP processing. They used physiological (0.8 mM, as normal control), low (0–0.4 mM), and high (1.2–4.0 mM) concentrations. In this study, low concentrations enhanced Aβ secretion and impairs cell viability, whereas high level of Mg promotes alpha-secretase cleavage pathway for APP processing (with subsequent increase in sAPPα synthesis, resulting from APP cleavage by α-secretase in sAPPα + α-CTF). The benefic effects of high Mg level, switching β-to α-secretase cleavage, can be partially related to intramembrane retention of APP (Yu et al., 2010). In contrast, low Mg levels are associated with low rate of intramembrane APP. More interesting, high rates of sAPPα demonstrate neuroprotective properties in different neuroglial stress conditions such as traumatic brain injury (Plummer et al., 2016), proteasomal stress (Copanaki et al., 2010) or proteotoxic stress-induced by BAG3 (Renziehausen et al., 2015). sAPPα also showed neurotrophic

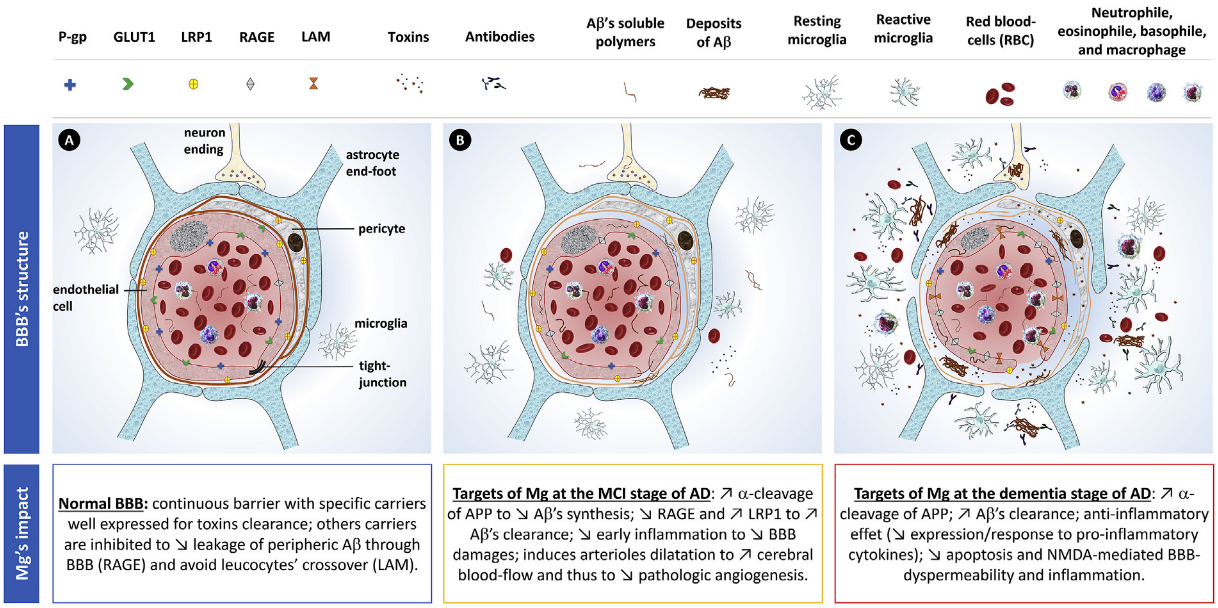


**Fig. 2. Blood-brain barrier (BBB) dysfunction in AD and potential targets of Mg.**
***A)* Normal BBB**: continuous barrier composed of luminal endothelial cells with tight-junctions, middle pericytes and basement membrane, with an over layer of abluminal astrocytes' end-foots. The perivascular space is tight and the paracellular diffusion restricted. Some specific transporters are well expressed for toxins clearance and filtration of serum substances addressed to neuroglia. Others carriers are inhibited to reduce leakage of peripheric Aβ through the barrier (RAGE carrier) and to avoid leucocytes' crossover (LAM). ***B)* MCI stage**: Aβ's dysmetabolism combined to altered cerebral blood-flow trigger the early impairments of BBB. The downregulation of some toxin clearance's carriers and a discreet basement membrane impairment are the main alterations, leading to subtle abnormal leakages and minimal inflammatory response of microglia. Mg is expected to prevent local excessive Aβ synthesis and to improve its clearance. The early inflammatory processes as well as the pathologic pro-angiogenic signaling should also be inhibited. ***C)* Dementia stage**: there are severe alterations of the main BBB's components: disruption of tight-junctions and basement membrane; endothelial cells' dysmorphism; astrocytes' end-foot retraction; downregulation of GLUT1, P-gp and LRP1; upregulation of RAGE and LAM. These disorders lead to a toxic leakage of blood substances and a substantial crossover of blood cells result in major neuroinflammation and oxidative processes in the neuroglial compartment. Aβ deposits originating from blood, endothelial cells and neuroglia play a critical role in the main processes. Mg is expected to inhibit the endothelial/neuroglial synthesis of Aβ as well as reducing the inflammatory/oxidative consequences of all the toxins. ***Abbreviations***: glucose transporter 1 (GLUT1), P-glycoprotein (P-gp), low density lipoprotein receptor-related protein 1 (LRP1), receptor for advanced glycation end products (RAGE), matrix metallopeptidase 9 (MMP-9), leucocyte adhesion molecule (LAM).

effect by reversing age-linked decline in neural progenitor cell proliferation (NPC) (Demars et al., 2013) as well as promoting proliferation and glial differentiation of adult hippocampal NPC (Baratchi et al., 2012). About the underlying mechanisms, using rat hippocampal organotypic slice cultures, Ryan and al concluded that the neurotrophic property of sAPPα involves a multi-level transcriptional response, including: upregulation of immediate early gene transcription factors (AP-1, Egr1), modulation of the chromatin environment, and apparent activation of the constitutive transcription factors CREB and NF-κB (Ryan et al., 2013).

About tau accumulation, in streptozotocin-induced sporadic Alzheimer's model of rats, Xu et al. (2014) found a neuroprotective effect of Mg sulfate. Their study demonstrated that Mg decreased tau hyperphosphorylation by increasing the inhibitory phosphorylation of Glycogen synthase kinase 3-beta (GSK-3β) at serine 9, thereby increasing the activity of Akt at Ser473 and PI3K at Tyr458/199 and also improving insulin sensitivity.

### 5.3. Toxins clearance through blood-brain barrier (BBB)

In AD, it is widely considered that vascular and BBB dysfunctions are often among earlier pathogenic changes before Aβ′s plaques and tau tangles (Merlini et al., 2011; Sweeney et al., 2019; Thal et al., 2003; Yamazaki and Kanekiyo, 2017). It is also admitted that vascular-cerebral interfaces' disturbances act in a vicious circle as a cause and/or a consequence of APP's dysmetabolism in AD (Anderson et al., 2011; Jefferies et al., 2013; Yamazaki and Kanekiyo, 2017). Indeed, the microvascular alterations can result from the inflammatory response of activated astrocytes and microglia to Aβ′s dysmetabolism. This inflammation is associated with an excessive angiogenic signaling mainly mediated by thrombin and vascular endothelial growth factor (VEGF) (Jefferies et al., 2013). These mediators secondary promote endothelial Aβ′s hypersecretion with subsequent prooxidative dysmetabolism and further endothelial/neuroglial damaging (Jefferies et al., 2013). It has also been postulated that the pathologic angiogenesis can be triggered by a primary alteration of cerebral blood-flow (CBF) due to arteriolar alterations, leading to an inappropriate upregulation of microangiogenesis (Jefferies et al., 2013). Otherwise, an excessive NMDA receptors-mediated increase of BBB's permeability is involved and is likely to be critical at mid and later stages of AD (Xhima et al., 2016). In humans, AD's early/late microvasculopathy occurrence is supported by several imaging studies (DCE-MRI, T2* and SWI MRI, FDG-PET and verapamil-PET), post mortem neuropathological findings and kinetic analysis of biofluid markers (mainly, albumin-leakage) (Sweeney et al., 2019). Additionally, in the usual AD's genetic animal models (including PSEN1, APP and APOE4 transgenic mice), a BBB dysfunction precedes Aβ/tau accumulation and brain atrophy (Sweeney et al., 2019). The BBB alteration affects perivascular astrocytic end-feet, pericytes, basement membrane and endothelial cells (Sweeney et al., 2019; Yamazaki and Kanekiyo, 2017). It results in abnormal paracellular/transcellular transfers through the BBB (Jefferies et al., 2013). The aberrant transcellular transfers are related to deregulation of specific transporters, implying a downregulation of glucose transporter 1 (GLUT1), P-glycoprotein (P-gp) and low density lipoprotein receptor-related protein 1 (LRP1) as well as an upregulation of the receptor for advanced glycation end products (RAGE), the matrix metallopeptidase 9 (MMP-9) and the leucocyte adhesion molecule (LAM) (Sweeney et al., 2019; Yamazaki and Kanekiyo, 2017). Importantly, the transcellular dyspermeability leads to microbleeds with a subsequent toxic perivascular accumulation of blood-derived substances like fibrin, thrombin, albumin, immunoglobulin G and hemosiderin (Yamazaki and Kanekiyo, 2017). The consequence is neuroinflammation, neuroglial membrane peroxidation and apoptosis (Jefferies et al., 2013; Sweeney et al., 2019). Furthermore, capillary deposition of Aβ polymers results in endothelial cells dysmorphism/dysfunction, capillary occlusion, thickening/disruption of basement membrane and alteration of interstitial space's configuration: it is the cerebral amyloid angiopathy (CAA) (Anderson et al., 2011; Jefferies et al., 2013; Thal et al., 2003). In summary, microvascular alterations in AD imply Aβ's dysmetabolism, proinflammatory signaling in response to Aβ hypersynthesis (neuroglial and endothelial), oxidative stress in endothelial cells, toxic leakages through BBB and finally, induction of neuroglial oxidative and apoptotic cascades (Fig. 2).

Against the pathogenic pathways of these processes, the promotion of APP's α-cleavage by Mg is a key-effect in anti-Aβ prophylaxis for microvascular and neuroglial preservation (Yu et al., 2010). Additionally, the ability of Mg to induce a microvascular smooth muscle's relaxation (Gröber et al., 2015) can significantly improve cerebral blood-flow, and thus, prevent the pathologic reactive angiogenesis. Moreover, the neuroglial/endothelial anti-inflammatory impact of Mg is reported in several studies cited above (Wang et al., 2017; Wolf et al., 2008; Yu et al., 2018). This ability to reduce the inflammation triggered by Aβ and toxins leaked through the BBB suggests that a Mg supplementation remains a useful option at later stages of AD. Aside from these potential pharmacodynamics, Mg can also improve endothelial functions. In this regard, Zhu et al. (2018) demonstrated how Mg supplementation could affect BBB permeability and its functions, and thus reduce neurodegeneration. According to these authors, this property is mainly based on its effects on Aβ protein's clearance through the barrier. Indeed, Mg accelerates the Aβ transcytosis via BBB from brain to blood side through low-density lipoprotein receptor-related protein (LRP) and phosphatidylinositol binding clathrin assembly protein (PICALM). On the contrary, it decreases the influx of Aβ to the brain side by its actions on receptor for advanced glycation end products (RAGE) and caveolae (Zhu et al., 2018).

### 5.4. Synaptic activity and energetic metabolism

In AD, synaptic dysfunction and synapses loss have a critical role in pathophysiology, especially during the early stages (Pozueta et al., 2013; Spires-Jones and Knafo, 2012). At these stages, the synaptic alteration consists in a decrease of dendritic arborization and a synaptic contacts' dysfunction. This alteration is mainly due to accumulation of soluble oAβ (oligomers of amyloid-β) before plaques' constitution (Cline et al., 2018; Price et al., 2014). The pathogenic role of oAβ has first been supported by the observations of Lambert and al (Lambert et al., 1998). They noted that synthetic oAβ (without fibril) induces a rapid inhibition of the synaptic transmission potentiation and then, neuronal loss. Later, numerous *ex vivo* and *in vivo* studies confirmed this hypothesis (Klyubin et al., 2008; Müller-Schiffmann et al., 2016; Shankar et al., 2008). The toxic effect of oAβ in AD is based on a signaling through cellular prion protein ($PrP^C$) and metabotropic glutamate receptor 5 (mGluR5) (Beraldo et al., 2016; Brody and Strittmatter, 2018). oAβ also acts by inducing phosphorylation of tau and inactivation of insulin receptor substrate (Ma and al., 2009). Considering that Mg can significantly reduce the toxic β-fragmentation of full-length APP (Yu et al., 2018), its prophylactic use is an interesting perspective for neuroprotection as soon as a mild cognitive impairment (MCI) is diagnosed. In this regard, Li et al. (2014), using APPswe/PS1dE9 mice (model of AD), found that early Mg-L-threonate treatment could prevent synaptic loss and β-processing of APP. Although MCI does not always evolve into dementia, it is associated with up to 15 times higher risk of AD developing (Burns and Iliffe, 2009). Thus, the use of Mg seems relevant to prevent this possible evolution by an early supplementation.

Another pathogenic factor in AD is the dysregulation of NMDA receptors (NMDARs) by Aβ-complexes (Deng et al., 2014; Dewachter et al., 2009; Mota et al., 2014; Snyder et al., 2005). NMDARs are glutamatergic excitatory channels with high calcium permeability and voltage-dependent channel block by Mg (Calabresi et al., 1992). Calcium influx in neurons is reduced by Mg at membrane voltages near rest, but the lock is removed by intensive membrane depolarizations (Hansen et al., 2018). The NMDARs are formed by variable association of seven types of subunits (GluN1, GluN2A-D, and GluN3A-B) combined into tetrameric complexes (Hansen et al., 2018). These receptors, especially most of those that are synaptic, with d-serine as coagonist, have a crucial role in neuroplasticity for synaptic facilitation and network developing, mainly via massive calcium influx signaling (Volianskis et al., 2015). The foremost process of neuroplasticity is synaptic potentiation, including an initial short-term potentiation (STP) followed by long-term potentiation (LTP), the ultimate and stable stage of network facilitation. STP requires two components: the faster mechanism involves activation of GluN2A and GluN2B subunits whereas the slower is related to GluN2B and GluN2D subunits activation. Later, LTP, requires activation of primarily triheteromeric NMDARs with GluN2A and GluN2B subunits. The synaptic activation of NMDA receptors with GluN2A-subunits is involved in non-amyloidogenic processing of APP by alpha-secretase amyloid precursor (Hoey et al., 2009) whereas GluN2B subunits promote Aβ synthesis by β-secretase (Hardingham and Bading, 2010). In contrast, extrasynaptic NMDA receptors (containing GluN2B-subunits), with glycine as coagonist, are mostly involved in long-term depression (LTD) and toxic processes related to acute brain injuries or neurodegeneration (Bordji et al., 2010; Hardingham et Bading, 2010). The extrasynaptic activation initiates a complex cascade of reactions follows ending up in excitotoxicity or non-excitotoxic apoptosis (Papouin and Oliet, 2014). Numerous studies showed that chronic activation of extrasynaptic receptors results in excessive Aβ synthesis (Bordji et al., 2010; Rush and Buisson, 2014). Some synaptic NMDA receptor with GluN2B-subunits type are also involved in this process (Hardingham and Bading, 2010). In AD, various abnormal pathways result in overexpression/overstimulation of extrasynaptic NMDARs as well as pro-excitotoxic activity of synaptic NMDARs (Kamenetz et al., 2003) (Dewachter et al., 2009; Mota et al., 2014; Pozueta et al., 2013; Wang and Reddy, 2017; Zhang et al., 2016). Indeed, Aβ accumulation has membrane prooxidative effects due to an increased production of hydrogen peroxide and hydroxyl radicals (Butterfield et al., 2010; Mota et al., 2014; Zhang et al., 2016). These alterations lead to membrane hyperexcitability and NMDA hyperactivity with subsequent excitotoxicity. The excitotoxic role of tau in AD implies its dendritic accumulation with an overstimulation of extrasynaptic NMDARs leading to more tau hyperphosphorylation (Zhang et al., 2016).

Therefore, several pharmacological researches target NMDA, but the efficacy of the developed drugs is limited by the aversive effects, the transient response with subsequent rebound-effect, and the narrow therapeutic windows. Interestingly, some relevant studies showed that both synaptic and extrasynaptic NMDA receptors are highly sensitive to channel block by extracellular Mg (Burnashev et al., 1992; Calabresi et al., 1992; Nikolaev et al., 2012; Wang and MacDonald, 1995). For note, the deep binding site of Mg for NMDA channel block is the same as memantine's (Glasgow et al., 2018). Memantine demonstrates some effectiveness in AD managing and is indicated in moderate to severe stages (Bond et al., 2012). Like memantine, Mg is expected to reduce NMDAR-mediated excitotoxicity and moreover, the β-processing of APP. Nikolaev et al. (2012) confirmed the NMDA-R block hypothesis, using high Mg levels to inhibit neuronal NMDA activity in hippocampal slices of rats. This inhibition, combined with APP-processing's modulation, can result in a substantial reduction of Aβ synthesis (Yu et al., 2010; Yu et al., 2018). In their study, Li et al. (2014) reported a significant downregulation of NMDAR signaling and a stabilization of β-secretase expression. Moreover, their findings suggested that high extracellular levels of Mg prevented the excessive Aβ-induced reductions in synaptic NMDARs by preventing calcineurin overactivation (Li et al., 2014).

Apart from synaptic regulation, Mg shows a neuroprotective effect against energetic dysmetabolism induced by chronic glutamate stimulation (as involved in AD pathogenesis). This property had been demonstrated in rat cortical neuron preparations already containing a physiological concentration of Mg and then exposed to excitotoxic level (100 μM) of glutamate (Clerc et al., 2013). In such conditions, Mg sulfate adding resulted in an improvement of the spare respiratory capacity of the neurons. This effect is all more interesting since Aβ accumulation in mitochondria is known to impair the respiratory chain in a deleterious cycle: dysfunction of complexes III and IV of the chain, then cytoplasmic calcium level increasing and oxidative stress as well as ATP down-production, and finally a worsening of calcium level and oxidative stress (Moreira et al., 2010).

## 6. Current limitations and research needs

Although well-conducted researches cited above report lower CSF Mg levels in AD patients, the clinical background on the effectiveness of this ion is weak. For now, the experimental findings are encouraging, but such results do not provide a strong value as the one of clinical investigations. First, in experimentation, animal models cannot reproduce exactly human conditions of AD (Chun et al., 2018). This limitation impairs the estimation of the real human cognitive impact and the anticipation of aversive effects possibly associated with the effective clinical doses. Moreover, it is a hard challenge to correlate *in vitro* neurochemical/neurohistological changes or animals' memory improvement with expected clinical results. Indeed, human relative therapeutic response depends on intricated specific factors (genetics and environmental determinants’) and neuroglial specificities (including neuronal networks and neurotransmission). Nevertheless, the current available data deserve more interest from clinical research teams since Mg is an endogenous substance and potentially targets much more neuroglial functions than any drug pharmaceutically developed against AD to date (Bond et al., 2012; Kamat et al., 2016; Wenzel and Klegeris, 2018). More interestingly, although the use of Mg in AD is not considered in human guidelines for now, its properties in various neurological pathologies demonstrate clinically a good tolerability and a robust impact on neuroexcitability and neuroglial survival (Trapani et al., 2011). The remaining challenge mainly lies in defining the optimal pharmacodynamics for this ion and evaluating its use in large human cohorts.

Above all, the potential neuroprotective effect of Mg is limited *in vivo* by its bioavailability, mainly its neuroglial availability. Indeed, systemic Mg is tightly regulated by a balance in intestinal absorption, glomerular filtration, tubular reabsorption and urinary excretion (Allgrove, 2009; Schmitz et al., 2005). Like most of circulating substances, Mg's transfer through BBB and blood-CSF barrier is also finely regulated, requiring mainly the transient receptor potential melastatin (TRPM), types TRPM6 and TRPM7 (Ghabriel et Vink, 2011). Therefore, supplementation's impact on neurons is limited, unless high doses are used. For example, for anticonvulsivant prophylaxis, a serum Mg level range of 4–7 mEq/L is required (normal range of 1.5–2.5 mEq/L) (Hunter and Gibbins, 2011). Considering the broad therapeutic window of Mg, high doses -probably– needed for AD are expected to be well tolerated by most of the patients. Intravenous administration is an interesting option to obtain a better serum availability and subsequent transfer through the brain barriers, but this solution is not preferable for long-term treatments. Another way, the intrathecal administration, could have been the ideal option for optimal bioavailability, but such approach usually requires a complex implantation procedure with high infection risk. It is therefore important to identify the optimal strategy that can result in high levels of Mg on the brain side of BBB. Otherwise, the adjuvant use of Mg should be evaluated. Indeed, most of the available anti-AD drugs demonstrated substantial anti-neurodegenerative properties, but pathophysiological pathways targeted are usually limited. Therefore, high doses are required but are thwarted by narrow therapeutic windows. In this line, Mg provides an interesting option to potentialize the main effects of a synthetic drug as well as to act against the pharmacodynamic targets uncovered by the considered drug. In any event, the therapeutic window related to Mg's availability in neuroglial environment should be carefully explored. Indeed, Yang and Ksiezak-Reding (1999) suggested that regional elevation of Mg and calcium can trigger pathological accumulation of paired helical filament tau (PHF-tau). Although this study was conducted *in vitro*, it points out that attention should be paid to aversive chronic effects of high versus moderate increase of Mg level in neuroglial environment. The methodology of the future dedicated studies should target the pros and the cons related to each option.

## 7. Conclusion

There are robust evidences supporting that Mg could be considered in AD prophylaxis for MCI cases and as an adjuvant option at later stages of AD. Indeed, several experimental findings show that this ion can inhibit the main pathophysiological processes involved in AD as well as the ones in other neurodegenerative diseases. However, since the clinical background of magnesium's effectiveness in AD remains poor, larger clinical studies are needed. Moreover, further basic studies are required to identify the best strategy for optimal pharmacokinetics and pharmacodynamics.

## Declarations of interest

None.


## Research funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.


## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.03.014.

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