REVIEW ARTICLE

Synaptic Elimination in Neurological Disorders

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Abstract: Synapses are well known as the main structures responsible for transmitting information through the release and recognition of neurotransmitters by pre- and post-synaptic neurons. These structures are widely formed and eliminated throughout the whole lifespan *via* processes termed synaptogenesis and synaptic pruning, respectively. Whilst the first process is needed for ensuring proper connectivity between brain regions and also with the periphery, the second phenomenon is important for their refinement by eliminating weaker and unnecessary synapses and, at the same time, maintaining and favoring the stronger ones, thus ensuring proper synaptic transmission. It is well-known that synaptic elimination is modulated by neuronal activity. However, only recently the role of the classical complement cascade in promoting this phenomenon has been demonstrated. Specifically, microglial cells recognize activated complement component 3 (C3) bound to synapses targeted for elimination, triggering their engulfment. As this is a highly relevant process for adequate neuronal functioning, disruptions or exacerbations in synaptic pruning could lead to severe circuitry alterations that could underlie neuropathological alterations typical of neurological and neuropsychiatric disorders. In this review, we focus on discussing the possible involvement of excessive synaptic elimination in Alzheimer's disease, as it has already been reported dendritic spine loss in post-synaptic neurons, increased association of complement proteins with its synapses and, hence, augmented microglia-mediated pruning in animal models of this disorder. In addition, we briefly discuss how this phenomenon could be related to other neurological disorders, including multiple sclerosis and schizophrenia.

1. INTRODUCTION

Synapse maintenance and elimination are essential mechanisms underlying synaptic plasticity in the central nervous system (CNS), as both processes are likely involved in learning and lifelong memory processing and storage [1-4]. Not surprisingly, these phenomena have been long known to rely on neuronal activity. In fact, studies from the 1970s demonstrated that monocular deprivation affected the decision regarding which synapses are kept or pruned [5-9]. Sensory deprivation significantly disrupts eye-specific segregation, with the intact eye occupying a much greater thalamocortical projection compared to the deprived one [8]. Meanwhile, pharmacological experiments clearly show that inhibiting one eye activity by tetrodoxin injection impaired eye-specific segregation in fetal cat dorsolateral geniculate nucleus (dLGN) [9].

Equally remarkable are the differences in the spatiotemporal regulation at which these events occur. Indeed, all brain regions experience a sharp increase in synapse formation at early post-natal stages, followed by a period of synaptic pruning [10, 11]. The pruning of overly produced synapses is highly important to maintain the stronger connections, while eliminating the weaker ones, ensuring adequate propagation of information. Interestingly, it has been shown that brain regions involved in sensory information, such as the thalamus, auditory and visual cortices, mature earlier than those responsible for higher cognitive processing, such as the hippocampus and the pre-frontal cortex [10-18]. While the first ones reach their adult levels at late childhood, with their pruning period spanning from mid-to-late infancy, the latter regions only do so at early adulthood, since synaptic elimination only surpasses synaptogenesis rates from puberty onwards [10, 11, 14].

Until the last two decades, little was known regarding the main mechanisms related to synaptic elimination. Perhaps, the most notable discovery in that matter has been the involvement of glial cells and immune molecules in its regulation [19-22]. Given the importance of this event throughout

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life, it is not surprising that interference in synaptic pruning regulation could lead to neuropathological alterations. This review aims to provide an updated view of the principal molecular mechanisms encompassing synaptic pruning, focusing later on its possible involvement in relevant neurological disorders.

1.1. Molecular Mechanisms of Synaptic Elimination

Synaptic pruning is a phenomenon that heavily relies on activity, with both long-term potentiation (LTP) and long-term depression (LTD) inducing morphological changes at the synaptic level [13, 23, 24]. While LTP promotes spine turnover and synapse stabilization [13, 25], LTD, on the other hand, leads to spine shrinkage and loss, enhanced varicosities turnover and their separation from dendritic spines (Fig. **1**) [13, 24, 26, 27]. It is worth mentioning that LTD can be induced by two distinct molecular mechanisms: N-methyl-D-aspartate receptor (NMDAR)-dependent and metabotropic glutamate receptors (mGluR)-dependent LTD [28]. In the NMDAR-dependent LTD (NMDAR-LTD), after glutamate activation of the receptor, there is a modest Ca^{2+} influx that triggers a yet-unknown intracellular kinase activation. This kinase phosphorylates the GluR2 subunit of α-amino-3-hydroxy-5-methylisoxazole propionic acid receptor (AMPAR) at Ser-880, leading to its endocytosis, thus reducing the amount of AMPAR available in the spine surface and leading to LTD. In addition, this Ca^{2+} influx activates calcineurin, which, in turn, activates the protein phosphatase 1 (PP1). PP1 dephosphorylates the AMPAR subunit GluR1 at Ser-845, strongly reducing AMPAR conductance [28]. On the other hand, mGluR-dependent LTD (mGluR-LTD) requires the activation of group I mGluRs (mGluRI), namely mGluR1 or mGluR5, members of the G-protein coupled receptor (GPCR) superfamily. Upon their activation, G_q and $G_{\alpha 11}$ proteins trigger a series of events ultimately leading to protein kinase C (PKC) activation. Then, PKC phosphorylates GluR2 also at Ser-880, prompting AMPAR internalization and LTD [28].

Interestingly, LTD-triggered spine shrinkage is reversed by the NMDAR antagonist APV and independent of AMPAR endocytosis [24,29]. Moreover, genetic deletion of GluN1 and GluN2B, two NMDAR subunits, promotes reduced spine density and impaired LTD in the cortex and hippocampus [30]. Notwithstanding, while NMDAR is involved in both LTD and spine shrinkage, biochemical evidence suggests these events are triggered by distinct signaling pathways (Fig. **1**) [24, 31]. More recently, Henson and colleagues [32] have demonstrated an augmentation in unpaired synapses upon NMDA application to mixed hippocampal and cortical cultures, providing extra evidence for the NMDAR role in synaptic elimination (Fig. **1**) [32]. On the other hand, an important role of mGluRI in LTD-mediated synapse elimination has been identified [33-35]. Surprisingly, it has been found that in mice lacking mGluR subtype 1 (mGluR1) not only is LTD impaired, but also these animals display deficits in surplus pruning of climbing fibers (CFs) synapses onto Purkinje cells (PCs) in the cerebellum [33, 34]. Moreover, mGluR1$^{-/-}$ and mGluR5$^{-/-}$ animals show higher synapse number than their wild-type (WT) littermates in the dLGN and layer IV of the cortical cortex, respectively [36, 37].
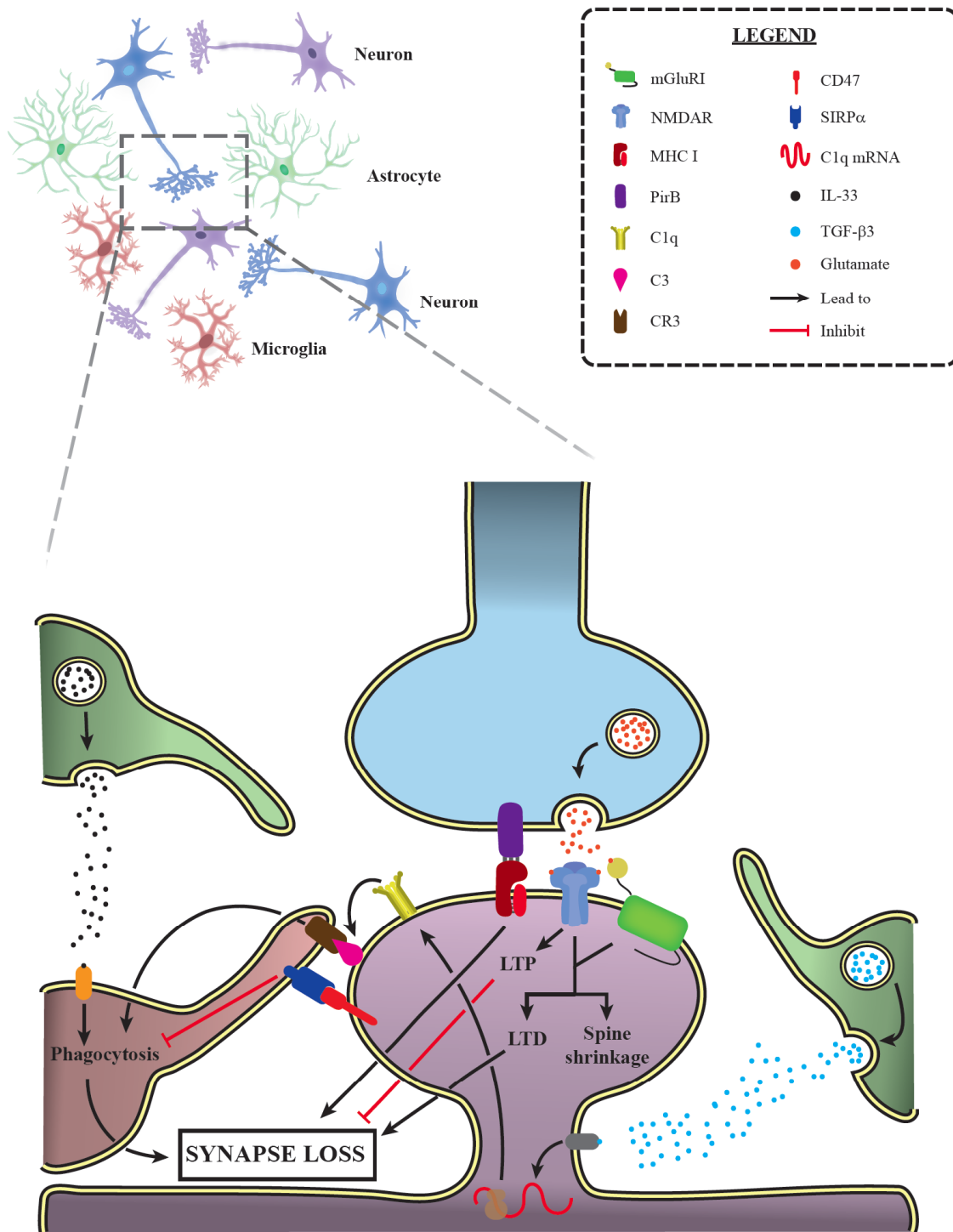
Pharmacological evidence also indicates that chemical LTD induction by mGluRI agonist application leads to an overall reduction in synaptic strength, followed by persistent synapse elimination (Fig. **1**) [38, 39]. Equally remarkable, this effect only happens when LTD is induced repeatedly.

Despite the relevance of these two types of LTD in mediating synaptic morphological changes, little is known about whether they act in concert to drive synaptic loss. Nonetheless, recent evidence shows that LTD weakens synapses with the ones with lower glutamatergic release probability being selectively eliminated in the following 7 days of stimulation, an effect that is spread to their closest neighbors [40]. In addition, NMDAR-dependent synaptic weakening and spine shrinkage occurs after 1 h of LTD induction. Notably, mGluRI activation is only required when this phenomenon occurs in large spines [41].

Even though the literature presents more evidence for mGluR- and NMDAR-LTD involvement in spine shrinkage and synaptic elimination, other molecular circuits take part in this process as well. For instance, semaphorins 7A and 5B are known to promote synaptic pruning while semaphorin 3A is thought to prevent it [42, 43]. Moreover, γ-aminobutyric acid (GABA)ergic inhibition has been proposed to be involved in synaptic loss during CFs elimination in the cerebellum and at puberty in the female hippocampus [44, 45]. Also, glutamatergic receptors δ1 and δ2 interact with neurexins in a process mediated *via* Cbln2 and Cbln1, respectively, promoting the formation and maintenance of synapses in the CNS [46, 47]. It is also worth citing the novel role played by the β-catenin/N-cadherin complex in the synapses. Throughout development, those spines that accumulate higher amounts of β-catenin/N-cadherin are preferably maintained and form stable spines, while those neighbor spines with lower levels of this protein complex are eliminated in an activity-dependent fashion [48]. These two proteins are also found pre-synaptically, functioning in the neocortex by stabilizing synapses and reducing their excessive turnover [49]. Despite having mentioned the main known mechanisms underlying synaptic pruning, additional mechanisms could also prove relevant (for more information on this topic, please refer to [1]).

1.2. Immune Molecules Play a Central Role in Glial-mediated Synaptic Pruning

The most notable recent finding concerning synaptic pruning is the discovery that immune molecules mediate synaptic elimination in the brain. Although erstwhile, the brain was considered an immune-privileged organ, at the dawn of the 21st century, it was shown that the immune system is involved in synaptic pruning. In a pioneer work, Huh and colleagues [50] argued that Class I Major histocompatibility complex (MHC-I) is expressed in neurons throughout the development in an activity-dependent manner, being necessary for adequate dLGN eye-specific segregation and sustained NMDAR-LTD. Later studies, aiming at understanding this phenomenon, have demonstrated that MHC-I molecules colocalize with dendritic spines and that MHC-I knockout (KO) animals display increased frequency of excitatory post-synaptic currents (mEPSCs) in both hippocampal

Fig. (1). Main mechanisms of synaptic elimination during development. Recent data have indicated a relevant role of immune molecules in developmental synaptic pruning. As it is shown here, astrocytes secrete TGF-β3, leading to the downstream upregulation of the complement component C1q by neurons. Once in the plasma membrane, C1q triggers the activation of the classical complement cascade later culminating in C3 accumulation, which is recognized by microglia *via* CR3, thus prompting the phagocytosis of target synapses. IL-33, another astrocytic-secreted factor, is essential for synaptic engulfment by microglial cells. In addition, MHC I and its binding partner PirB have been demonstrated to promote synaptic elimination, while pre-synaptic CD47 signals *via* SIRPα, inhibiting synaptic uptake by microglial cells. Finally, LTD induction, following NMDAR and group I mGluRs activation, is also capable of promoting synapse loss, while LTP inhibits this phenomenon. mGluRI: group I metabotropic glutamate receptor; NMDAR: N-methyl-D-aspartate receptor; MHC I: major histocompatibility complex class I; PirB: paired immunoglobulin-like receptor B; CR3: complement receptor 3; CD47: cluster of differentiation 47; SIRPα: signal-regulatory protein α; IL-33: interleukin 33; TGF-β3: transforming growth factor β3. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

and visual cortical neuronal cultures [51]. This phenomenon is accompanied by an increase in pre-synaptic terminal buttons size and vesicular number, which, according to the authors, could reflect altered synaptic scaling in MHC-I KO animals. In addition, mice lacking two MHC-I molecules, H2-D^b and H2-K^b, has been demonstrated to display impaired visual cortex and dLGN synaptic plasticity and eye-specific segregation [52-54]. Strikingly, this phenotype is accompanied by disrupted synaptic elimination and impaired LTD, which is rescued by inducing H2-D^b expression (Fig. **1**) [53]. Accordingly, blockade or complete deletion of PirB, an MHC-I receptor, phenocopies the elevated spine density and LTD impairments observed in the visual cortex and hippocampus of MHC-I KO animals (Fig. **1**) [55-58]. Albeit these findings are observed in younger animals during specific periods, evidence suggests that these MHC molecules and PirB are later upregulated in microglia and neurons, especially during aging [59]. Thus, these MHC molecules appear to play a role in synaptic plasticity during learning processes, memory formation and aging, events closely associated with synapse turnover [4]. Furthermore, it is worth mentioning that MHC-I molecules are found to colocalize with the complement component C1q, another immune factor widely involved in synaptic elimination and expressed at the same developmental periods throughout mice lifespan [54, 60].

The direct involvement of the classical complement cascade in synaptic pruning has been elegantly demonstrated firstly in the dLGN [19]. Throughout the development, immature astrocytes secrete transforming growth factor β3 (TGF-β3) [20], leading to upregulation of all C1q subunits in retinal ganglion cells (RGCs) (Fig. **1**), with C1q localizing in close proximity with dendritic spines during the peaking pruning period [19]. When C1q is knocked out, mice display deficient dLGN eye-specific segregation due to impaired synaptic elimination [19]. This phenotype has been replicated in KO animals for C3, a protein downstream of C1q in the classical complement cascade and also found to colocalize with synapses (Fig. **1**). Since activated C3 is recognized by the complement receptor 3 (CR3), which is solely expressed in microglia in the brain parenchyma, and that microglia makes contact with synaptic structures [21], it has been hypothesized that surveillant microglia might be implicated in synaptic pruning [22] (Fig. **1**). In fact, microglial cells actively engulf C3-tagged synapses, a phenomenon dependent on neuronal activity, given that intraocular injection of TTX elevated microglia-mediated pruning [61]. Interestingly, microglial CR3 activation has also been associated with LTD induction, further adding evidence for the complement involvement in synaptic plasticity [62]. In addition, biochemical investigations suggest that complement-mediated pruning is probably associated with apoptotic-like mechanisms [63-66].

These studies opened up an avenue of investigation aiming at demonstrating that microglia is a key player in this synaptic plasticity mechanism. For instance, mice bearing homozygous deletion for the CX3CL1 receptor (CX3CR1), exclusively found in microglia, display delayed synaptic elimination in the hippocampus, which is accompanied by long-lasting electrophysiological and behavioral deficits [67,

68]. This observation could be in part explained by the reduced number of microglial cells multiplying or migrating into the CA1 region during the synaptic pruning period, although it is also possible that disrupted apoptotic-like mechanisms play a role as well [67, 69]. Moreover, loss of progranulin (GRN) in microglia, a protein involved in lysosomal and autophagy cargo degradation [70, 71], leads to increased synaptic pruning in thalamocortical circuits [70]. Interestingly, microglial cells are more activated in GRN KO mice, leading to increased C1q and C3 secretion, which could account for the excessive synaptic elimination observed. On the other hand, elevated GRN levels block synaptic pruning, with mice displaying higher synaptic density in the hippocampus [72]. Similar findings are observed in mice deficient for Atg7, a protein required for autophagy, suggesting that this process is also needed for efficient microglia-mediated synaptic pruning [73]. Also, it is relevant to take in consideration that microglial activities are dependent on astrocyte-secreted interleukin 33 (IL-33), as animals deficient in this protein have disrupted synaptic elimination (Fig. **1**) [74]. Furthermore, microglial cells also play important roles in synapse formation throughout development, since animals depleted of this cell type display significant electrophysiological and synaptogenic impairments [75].

In addition, other studies have also fostered the investigation of new immunological signaling pathways in this phenomenon. Recently, CD47, a transmembrane immunoglobulin superfamily protein, has been shown to act as a protective signal preventing synaptic engulfment by microglia (Fig. **1**) [76]. This protein localizes preferentially at pre-synaptic terminals of more active synapses, signaling to microglial cells *via* SIRPα (Fig. **1**). Meanwhile, Bjartmar and colleagues [77] have provided the first evidence for neuronal pentraxins (NPs) participation in synaptic elimination. Deletion of NP-1, NP-2 and NP receptor (NPR) leads to increased synaptic numbers in the dLGN [77]. Notwithstanding, according to Koch and Ullian [78] these unpruned structures are comprised mostly of silent synapses, which do not contain AMPAR receptors, being unable to display AMPAR-mediated transmission and, hence, exhibit defective synaptic maturation. Another group of molecules thought to render synapses more mature in this context are the C1q-like proteins (C1qls) [79, 80]. These proteins signal *via* BAI3 in the CNS [80] and promote synapse formation and maintenance in the medial pre-frontal cortex (mPFC), since knocking down their expression levels leads to significant synaptic puncta reduction [79]. Surprisingly, a deeper inspection of the transcriptomic data produced by Chen *et al.* [81] indicates that NPs are upregulated in the CA1-CA3 hippocampal regions during LTP, while C1ql1 show significant downregulation. At first, this data seems odd, as LTP is implicated in synapse stabilization [25]; nevertheless, it is also possible that NPs and C1ql1 are involved in the elevated synaptic turnover observed in this phenomenon [24].

Perhaps one of the most curious findings concerning microglial participation in synaptic plasticity mechanisms has come from the work developed by Weinhard and coworkers [82]. By analyzing the CA1 region of the hippocampus in newborn mice at post-natal day 15 (P15), these authors have identified that microglial cells do not phagocytose the whole

synapse. Instead, these cells only engulf and uptake pre-synaptic material in a process of partial phagocytosis, so-called trogocytosis, in a complement-independent fashion. Additionally, microglia promote the protrusion of new filopodia from mature dendritic spine contacts [83]. Despite the novelty of this work, it should be taken with caution. First of all, the lack of complement-mediated synapse removal might be an exclusive feature of the CA1 region in the hippocampus. Indeed, this seems to be the only region protected from age-dependent synaptic density decline in the whole hippocampus [84]. Moreover, for all other hippocampal regions, deletion of C3 rescues this phenotype, suggesting a prominent role of the classical complement cascade in developmentally regulated synaptic elimination. Finally, other mechanisms could replace microglia-mediated spine engulfment in CA1. For example, astrocytes have been shown to prune synapses *via* MERTK- and MEGF10-mediated phagocytosis in the dLGN [85] and it is still unclear whether this phenomenon takes place in the hippocampus as well.

Since disruptions in synaptic pruning have been associated with an increased burden in neurological disorders, in the next sections, we are going to concentrate our discussion in the evidences for its involvement in the neuropathological alterations observed in Alzheimer's Disease (AD), Multiple Sclerosis (MS) and Schizophrenia (SCZ). Our major focus will be given to findings implicating immunological factors and glial cells as driving forces for altered synaptic elimination in each one of these diseases.

2. SYNAPTIC PRUNING IN NEUROLOGICAL DISORDERS
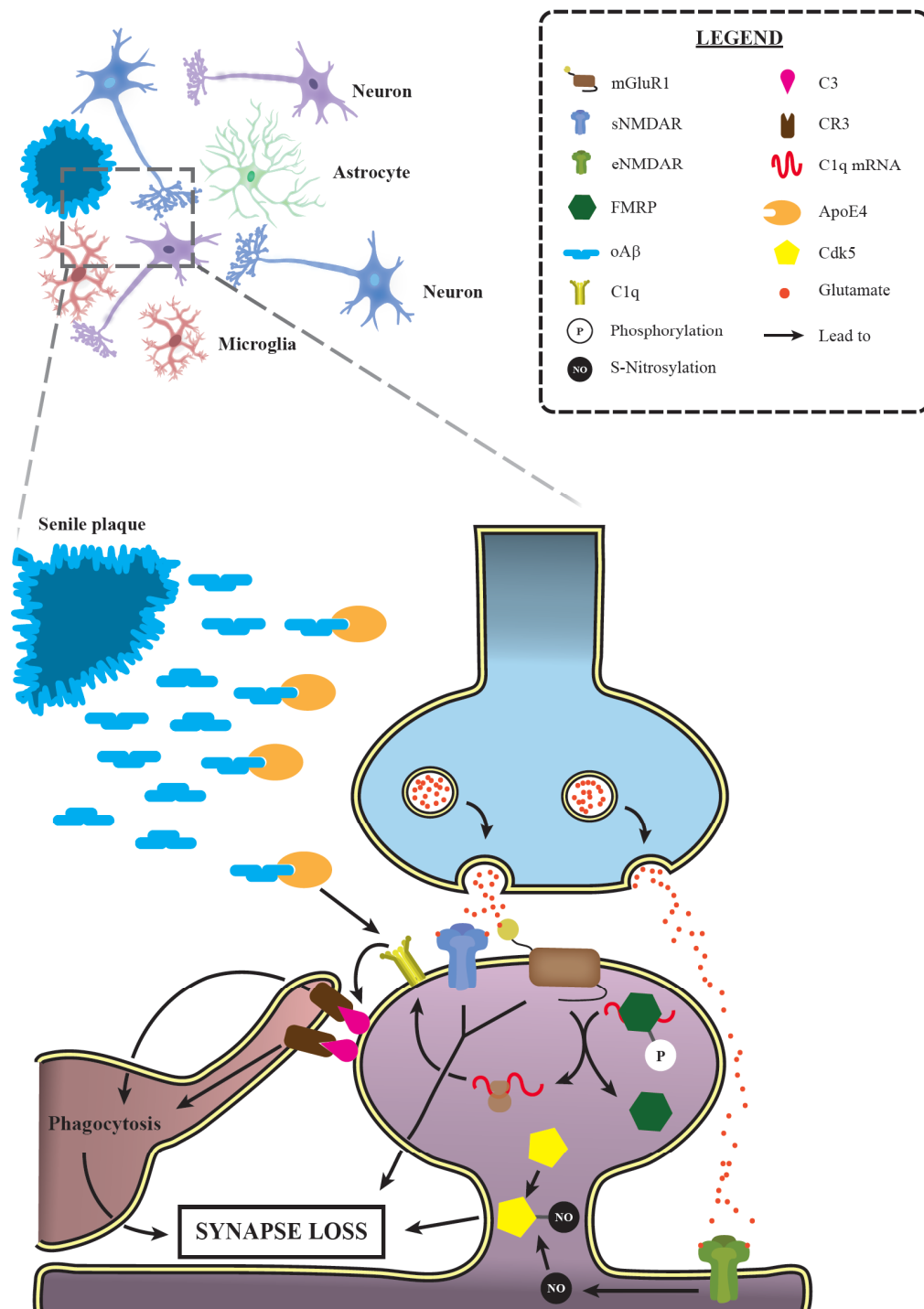
2.1. Alzheimer's Disease

Dementia is a syndrome that affects approximately 50 million people worldwide and its most common cause is AD, which responds for 60-70% of all cases [86-88]. The first case of AD was described by the German psychiatrist Alois Alzheimer, who identified the symptoms as progressive cognitive impairment, memory loss, language disability, spatial and temporal disorientation, hallucinations and delusions [89]. This disease is also characterized by evident cerebral atrophy and neurodegeneration, affecting cortical and subcortical regions, with greater synapse than neuronal loss [90-96]. Additionally, other hallmarks of AD found in the brain of affected patients are extracellular senile plaques, intraneuronal neurofibrillary tangles, gliosis, microglial activation and neuroinflammation [97-105].

These senile plaques are the result of oligomeric amyloid β (Aβ) peptide aggregation. Cleavage of amyloid precursor protein (APP), a cell surface receptor [106], occurs naturally in the brain, generating soluble APPα when APP is processed by α-secretase [107]. However, cleavage of APP by β-secretase and γ-secretase leads to the production of pathogenic Aβ forms of 40 and 42 amino acid residues, termed $A\beta_{1-40}$ and $A\beta_{1-42}$, respectively [108-110]. The presence of a qualitatively altered allele of γ-secretase results in higher production of $A\beta_{1-42}$, which is more susceptible to aggregation and toxicity [111] and is associated with higher pathogenicity compared to $A\beta_{1-40}$, which is the most abundant isoform produced in healthy brains [112].

Interestingly, the load of soluble oligomeric Aβ has been implicated in the synaptic loss observed in AD patients, even enabling the distinction between them and subjects with profuse plaques and tangles but with no symptoms of dementia [113]. Studies employing AD mouse models have shown that increased levels of soluble Aβ correlate with the decrease in synaptic density [114]. Notably, soluble Aβ represents the main factor contributing to the synaptotoxic and neurotoxic effects observed in AD [115, 116], leading to severe impairments in synaptic plasticity [117-120]. These oligomers are responsible for blocking hippocampal and cortical LTP [119-123], while also inducing LTD [119, 120, 124, 125], spine and neuronal loss [120, 125, 126]. The underlying mechanism appears to involve changes in glutamatergic neurotransmission mediated mainly by mGluRI and NMDAR (Fig. **2**). Further studies have demonstrated that the activation of NMDAR localized extrasynaptically (eNMDAR) is an important event involved in Aβ synaptic toxicity [117, 120, 124, 126-128]. This activation of eNMDAR triggers nitric oxide (NO) production in neuronal cultures exposed to Aβ oligomers [129]. In turn, NO promotes Cdk5 activation *via* S-Nitrosylation and its downstream signaling cascade leads to spine loss (Fig. **2**) [130]. Injection of these forms of Aβ in rodents has been proven as a useful model of mimicking synaptic pathology and by extension, the cognitive deficits found in AD [131-134]. These findings further reassert the role of soluble Aβ forms in the synaptic changes key to the etiology of AD.

Early synaptic loss is well established as a key feature of AD. For instance, studies have shown 38%, 14% and 44-55% reduction in the number of synapses in biopsies of AD patients at the temporal and frontal cortices and the hippocampus, respectively [94, 135-138]. Since then, other studies using distinct approaches endorsed the central role of synaptic loss in the pathology of AD. Further analysis using *post-mortem* tissues from AD patients confirms a decline in the synaptic number in the temporal, parietal and frontal lobes [139-141]. Also, a reduction of synaptic contacts have been noticed in the outer molecular layer of the hippocampal dentate gyrus, the CA1 region and the precuneus [142]. Moreover, presynaptic protein levels can also be used to estimate synaptic terminal loss [143]. The expressions of proteins such as synaptophysin, syntaxin, secretoneurin, PSD95 and glutamatergic vesicular transporters and receptors are shown to be significantly diminished in AD patients and in animal models [113, 144-150]. Notably, this PSD95 reduction has been shown to be driven by degradation *via* proteasome, a process mediated by NMDAR activity and that takes place exclusively at glutamatergic synapses [151]. A correlation between the cognitive shortcoming of AD patients and reduced expression level of synaptic proteins such as synaptobrevin, synaptotagmin and Rab3a has also been described [152], although results obtained in different studies may vary according to brain region and protein analyzed [143]. Furthermore, it has been suggested that synaptic loss is the strongest correlate with the cognitive deficits found in AD and might be a process restricted to excitatory synapses [147, 148, 150, 151, 153-155].

Neurofibrillary tangles (NFT), another key feature of AD, are mainly made of paired helical filaments of the

Fig. (2). Activation of synaptic pruning mechanisms is relevant for AD progression. Progressive synaptic loss is one of the main morpho-logical features of Alzheimer's disease, observed even earlier than senile plaque deposition. Several studies have demonstrated the prominent role of the classical complement cascade in such event. Indeed, it has been shown that ApoE4, a major AD risk factor, leads to C1q accumu-lation in animal models. Additionally, mGluR1 activation allows a greater C1q mRNA translation by promoting the dephosphorylation of FMRP, an RNA-binding protein that represses translation. These data provide a suitable explanation for the increased levels of C1q and its downstream complement factor C3 in AD, which, in turn, trigger targeted synapses phagocytosis by microglial cells. Moreover, NMDAR and group I mGluRs activation have also been involved in the excessive synaptic loss observed during AD. Interestingly, the activation of extra-synaptic NMDAR (eNMDAR) induces the production of the S-nitrosylation of Cdk5, another factor implicated in AD excessive synaptic elimination. mGluR1: metabotropic glutamate receptor 1; sNMDAR: synaptic N-methyl-D-aspartate receptor; eNMDAR: extrasynaptic N-methyl-D-aspartate receptor; FMRP: fragile X mental retardation protein; oAβ: oligomeric amyloid β; CR3: complement receptor 3; ApoE4: Apolipoprotein E ε4; Cdk5: cyclin-dependent kinase 5. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

phosphorylated microtubule-associated protein tau (MAPT). This MAPT causes the expansion of senile plaques and exacerbates the formation of plaque-associated dystrophic neurites containing its misfolded form [156]. In addition, NFT located in pyramidal neurons correlates with changes in morphology and decreased the density of dendritic spines [157]. Nonetheless, previous reports indicate that accumulation of MAPT at spines, rather than NFTs, are linked to the onset of tau-related pathologies in AD [101, 102, 158-162]. Accordingly, oligomeric Tau promotes the reduction of synaptic markers and impair mitochondrial function [162]. These effects are mediated *via* Tau relocation from axons to dendrites upon its phosphorylation [159]. Indeed, Hoover *et al.* [159], using a transgenic model mimicking Tau phosphorylation *in vivo*, have shown that this post-translational modification leads to LTP and memory formation impairments. Moreover, they have observed that hyperphosphorylated Tau dissociates from microtubules and is mislocalized to dendritic spines. This leads to reduced AMPAR and NMDAR surface levels in these structures, impairing appropriate glutamatergic transmission, which could account for the observed phenotypes and synapse loss often found in AD models even before NFT deposition [159]. Interestingly, this role of Tau in modulating synaptic plasticity is required for Aβ-induced synaptic defects, with both proteins being found at the same post-synaptic compartment [158, 160, 163]. Intriguingly, reducing Tau levels in a dose-dependent manner in a mouse model of AD has been shown to be neuroprotective, significantly dampening Aβ-excitotoxic effects by preventing NMDAR and PSD95 uncoupling, thus securing proper LTP induction, preventing neuronal loss and improving memory formation and locomotor coordination in behavioral tests [161, 164].

2.1.1. Overheating the Developmental Engine in AD: When Complement-mediated Synaptic Pruning Becomes Harmful

It is well known that AD etiology shares environmental and genetic risk factors [165-166]. The majority of the cases of AD are sporadic and affect elder individuals (Late Onset AD, abbreviated as LOAD), while the remaining, which is about 5% of the cases, have an autosomal dominant inheritance pattern, occurring before 65 years of age (Early Onset AD, shortened as EOAD) [167]. It has been shown that in several EOAD patients, there is greater expression and release of Aβ$_{1-42}$ peptide, which aggregates more rapidly in insoluble amyloid fibrils [168-171], frequently giving rise to the brain plaques that characterize the disease [172]. In addition, the risk of developing AD is highly associated with the expression pattern of distinct isoforms of the apolipoprotein E (ApoE) gene in both EOAD and LOAD patients, whose protein product binds with high avidity to Aβ (Fig. **2**) [173-175]. Indeed, while the presence of ApoE2 allele is protective [176, 177], the number of ApoE4 allele copies is proportional to the risk of developing LOAD and inversely correlated with the age of onset and years of survival [174-176, 178]. Moreover, recent research has also demonstrated that the ApoE4 isoform stimulates greater APP transcription compared to other isoforms, thereby increasing Aβ levels [179]. Also, homozygous ApoE4 carriers display elevated production of Aβ oligomers, which might be implicated in dendritic spine dysfunction and severe memory impairment

[180]. Several lines of evidence indicate that ApoE is highly relevant to AD development, making this gene a suitable candidate to study synaptic loss in this disorder. Using transgenic mouse models expressing distinct human ApoE alleles, authors have shown that the ApoE4 isoform produces the greatest reduction in both pre- and post-synaptic markers density, dendritic spine number and dendritic arbor complexity in the cortex, amygdala and hippocampus [181-186]. Furthermore, transcriptomic data obtained from human induced pluripotent stem cells (hiPSCs)-derived neurons bearing the ApoE4 allele indicates that genes involved in synaptic regulation are among those most differently expressed compared to those of ApoE3 neurons [187]. Amongst them, C1ql3 and neuronal pentraxin 2 are downregulated in ApoE4 neurons, which is very interesting as these genes might be involved in synaptic elimination. Likewise, distinct ApoE alleles have been found to interfere with astrocytic synaptic pruning capacity [188]. Interestingly, murine astrocytes expressing the human ApoE2 isoform show greater synapse phagocytosis compared to those cells expressing ApoE3 and ApoE4, with the latter displaying the lowest engulfment index [188]. This compromised ability of astrocytes in eliminating senescent synapses by ApoE4 mice leads to the accumulation of C1q in the hippocampus, especially in aged animals (Fig. **2**). If this augmented C1q targets senescent synapses, this could trigger higher synaptic engulfment by microglia. However, more studies will be needed to clarify this issue. It is also important to mention that early reports indicate enhanced microglial activation in an ApoE4 dose-dependent manner, with AD homozygous individuals displaying greater numbers of activated microglia in the frontal and temporal cortices compared to homozygous ApoE3 patients [189]. Taking in consideration that Aβ comprises an inflammatory stimulus to the brain [190, 191] and that ApoE4 microglia exhibit increased activation [189] and augmented levels of proinflammatory transcripts [187], these data argue in favor of a prominent role for ApoE4 in mediating neuroinflammation in AD.

Neuroinflammatory mediators have also been associated with the pathology of AD. The presence of the membrane attack complex (MAC) and the immune activation of microglia have been shown to be better correlated with the number of synapses than the load of neurofibrillary tangles and Aβ deposition [192]. Another finding worth mentioning is that the decreased level of complement defense 59, a protein that prevents MAC assembly, in the cortex and hippocampus of AD patients correlates with the reduction in synaptophysin [193]. These data further highlight the association of the complement system and AD development. In addition, previous reports indicate that C1q and C3, two components of the classical complement cascade, display age-dependent upregulation in the hippocampus and cerebral cortex [194]. This rise in C1q and C3 levels is even greater in AD models, suggesting their involvement in disease progression (Fig. **2**). Indeed, genetic deletion of C1q and C3 in AD mouse models promotes reduced neurodegeneration, plaque deposition, gliosis, and microglia activation, as well as increased expression of synaptic markers [195, 196].

Later studies helped to clarify the association between synaptic loss and reactivation of the synaptic pruning process during the course of AD [197]. For instance, Hong and col-

leagues [198] have demonstrated the detrimental role of the complement system and microglia in AD early synaptic loss. Increased deposition of C1q and C3 at synapses of hippocampus and cortex is observed in the human APP (hAPP) transgenic mouse model of AD, leading to accentuated synaptic engulfment by microglial cells before the onset of plaque deposition (Fig. **2**). This effect is mediated by oligomeric Aβ, since its intracerebroventricular injection prompts the deposition of C1q and C3 in the hippocampus of WT mice [198]. In contrast, ablation of the complement receptor CR3 reduces the synaptic loss and the number of phagocytic microglia [198]. Similar results are observed in Tau-P301S transgenic mice [199]. In these animals, neurodegeneration and hippocampal atrophy are present only after 12 months of age, while gliosis and synaptic dysfunction are detected in 6-month-old animals. Proteomic data indicate progressive accumulation of C1q at synapses, especially at the post-synaptic compartment, at the same age it is possible to identify excessive hyperphosphorylated Tau in these structures [199]. This evidence led the authors to hypothesize that the reduction in synaptic markers in the hippocampus is related to exaggerated pruning by microglial cells. In fact, this has been shown to be the case, as treatment of cultures with anti-C1q antibody inhibited microglia-mediated synaptic elimination. In contrast, other proteomics studies failed to identify the enrichment of complement components in the hAPP mouse model and in AD patient *post-mortem* brain samples [200, 201]. These contradictory data indicate that more studies should be conducted to fully clarify the role of the complement cascade in AD, aiming at distinguishing whether the progressive C1q accumulation at synapses, found by Dejanovic *et al* [199], is a sole consequence of the disorder or is also affected by the aging process.

Remarkably, Litvinchuk *et al* [202] have provided the first evidence for the participation of C3a, one of the two C3 cleavage products, and its cognate receptor C3aR in AD synapse loss, using the Tau-P301S mouse model. While C3b acts as an opsonin and signals *via* CR3 in microglia, C3a is usually implicated in triggering inflammatory signaling (for more information about AD neuroinflammation and the classical complement cascade, refer to [203]). In this study, genetic deletion of C3aR has led to a significant reduction in astrogliosis and microgliosis, while also rescuing LTP deficits, enhancing synaptophysin and PSD-95 levels and blocking neurodegeneration in the hippocampus. In addition, authors have also shown that C3a rendered microglia more activated, as indicated by enhanced synaptic markers uptake and CD68 staining, an effect attenuated in the double mutant (C3a KO/Tau-P301S) mouse model. It is also important to mention that C3a/C3aR pathway disruption in the Tau-P301S mice reduces tumor necrosis factor α (TNF-α), IL-1β and IL-6 back to WT levels [202]. Moreover, in the same study, RNA-seq analysis revealed that both microglia and astrocytes display neurotoxic features, a phenotype partly rescued by C3aR deletion. Interestingly, this microglial transcriptomic profile corroborates the data found by Karen-Shaul *et al* [204], indicating that during AD progression microglial cells assume a more proinflammatory and activated profile, thus contributing to the neuroinflammation observed in this disorder. On the other hand, the astrocytic transcriptomic profile partially resembles the features of A1 reactive

astrocytes characterized by Liddelow and collaborators [202, 205]. A1 astrocytes are shown to impair synaptic formation and neuronal electrophysiological properties, while also upregulating C3 mRNA levels [205]. Given that microglial cells are the major source of C1q in the brain [206], that this protein is accumulated in AD mouse models and the proinflammatory profile displayed by microglia in AD, one could suppose that these activated microglia could lead to the formation of reactive A1 astrocytes [205]. These two neurotoxic glial cells could be, at least in part, responsible for both the synaptic defects and neurodegeneration observed in AD. Finally, recent data indicate a prominent role for mGluR1 activation in increasing C1q expression at dendritic spines, favoring their uptake by microglial cells in the hippocampus of mice injected with $Aβ_{1-40}$ oligomers [207]. This phenomenon relies on fragile X mental retardation protein (FMRP) dephosphorylation, allowing local translation of FMRP-silenced mRNAs (Fig. **2**). Since mGluR1 activation is also involved in LTD induction, this data provides important evidence connecting LTD and complement-dependent synaptic elimination. Altogether, these results suggest a prominent role of the complement cascade in mediating early synaptic loss in AD.

2.1.2. Other Synaptic Pruning-related Molecules also Contribute to Exaggerated Synaptic Loss in AD

Other synaptic pruning-related molecules have also been established as contributors to AD development. For instance, caspase-3, a classic proapoptotic factor, is elevated in AD brains, being specially enriched at the post-synaptic density [208]. In line with this evidence, D'amelio *et al* [209] have demonstrated that caspase-3 triggers AMPAR dephosphorylation *via* calcineurin in an AD mouse model, without any obvious cell death. This reduction of AMPAR at spines leads to increased LTD and diminished hippocampal apical dendritic spine levels in 3-month old mice, triggering subsequent learning and memory deficits [209]. These abnormalities are rescued by intrahippocampal administration of the caspase-3 inhibitor, z-DEVD-fmk, suggesting the participation of apoptotic-like mechanisms in AD early synaptic elimination and making this pathway an interesting target for future therapeutic interventions. On the other hand, the human ortholog of PirB, LilrB2, comprises a high affinity Aβ receptor [210]. This MHC-I receptor also mediates altered synaptic plasticity and memory deficits often observed in AD models. Indeed, its genetic deletion in mouse hippocampal slices rescues LTP induction by oligomeric Aβ. Moreover, transgenic AD animals with PirB ablation perform better in memory tasks, compared to diseased animals bearing intact PirB copies. In contrast, IL-33 is reduced in AD patients' brains [211]. Interestingly, when this cytokine is administered to hAPP mice, it rescues LTP induction, while also improving Aβ clearance by microglia, making IL-33 an interesting therapeutic target [212]. Despite IL-33 importance in inducing microglia-mediated synaptic pruning, its effects might not be specific to this phenomenon, as IL-33 may simply activate microglial phagocytic capacity, which could explain why this cytokine is able to enhance Aβ uptake and degradation.

Neuronal pentraxin 1 (NP-1), progranulin (GRN) and the CX3CL1/CX3CR1 also take part in AD neuropathological

events. NP-1 levels, for example, are elevated in the hippocampus and plasma of AD individuals [213]. Likewise, NP-1 is upregulated in neuronal cultures treated with Aβ, where it mediates cell death and reduction of synaptophysin levels [214]. Intriguingly, progranulin levels in the blood and cerebrospinal fluid (CSF) increase with disease progression, correlating with cognitive decline and memory disturbance [215, 216]. Despite this, genetic deletion of GRN in hAPP mouse models worsens cognitive behavior, also leading to elevated numbers of activated microglia in the hippocampus, higher TNF-α and IL-1α mRNA levels and increased deposition of C1q at dendritic spines [217, 218]. This effect seems to be mediated by microglial cells, as specific deletion of GRN in this cell type leads to increased plaque burden and decreased phagocytic index [217]. In contrast, overexpression of this molecule prevents Aβ-mediated cell toxicity, diminishes plaque deposition and rescues neurodegeneration and memory deficits [217]. Therefore, these data may indicate that increased progranulin levels throughout the course of AD might reflect an attempt to reestablish the proper homeostatic process by increasing microglial clearance of Aβ, thus diminishing plaque accumulation. On the other hand, the role of CX3CL1/CX3CR1 is less well defined. While CX3CL1 is downregulated in the CSF and brain of AD patients, no change has been reported for its receptor level compared to healthy individuals [219, 220]. Moreover, deficiency in either membrane-anchored CX3CL1 or in its receptor increases Aβ phagocytosis, reducing plaque deposition [221, 222]. However, the lack of CX3CR1 has been shown to increase Tau pathological effects *via* elevated p-Tau levels [220, 221]. In addition, literature data are controversial regarding the activation status of CX3CR1^{-/-} microglia in AD. While Lee and colleagues [222] report reduced microglial activation and TNF-α mRNA levels in APP/PS1;CX3CR1^{-/-} mouse model, Cho *et al* [220] demonstrate the opposite in hAPP;CX3CR1^{-/-} mice. Therefore, what is the precise role of CX3CL1/CX3CR1 in AD neuroinflammation is still a matter of debate, while its role in AD synaptic elimination remains insofar unknown. Taken together, these data support the involvement of several modulators of synaptic elimination in AD progression.

Despite the vast majority of studies aiming at understanding synapse loss in AD has focused on investigating elevated synaptic elimination, an interesting alternative hypothesis that might explain the reduced synapse numbers observed is disrupted synaptogenesis. Interestingly, researchers have found that soluble Aβ leads to increased pre-synaptic Ca^{2+} levels, promoting higher phosphorylation levels of Ca^{2+}/calmodulin-dependent protein kinase IV (CaMKIV) and, ultimately, impairing activity-dependent synaptogenesis [223]. In addition, Levi *et al.* [224] demonstrated that human ApoE4 transgenic mice display deficient environmental-stimulated synaptogenesis, resulting in learning and memory formation deficits, compared to human ApoE3 transgenic mice. These evidences imply that impaired synaptogenesis could also play an important role in AD development and progression. However, whether the reduction in synapse number observed in this disease is due to diminished synapse formation, increased synaptic elimination or both is a matter that remains to be investigated.

Given the importance of synapse loss in AD development, therapies aiming at restoring normal synaptic levels or preventing their loss could benefit individuals affected by this disorder. For example, using a gene delivery system, Kampen & Kay [225] overexpressed progranulin in an AD transgenic mouse model. In this study, it is possible to observe that GRN expression leads to reduced Aβ plaque burden, astrogliosis and microgliosis, as well as increased synaptic density in the hippocampus. In another report, daily injections of the Heat-shock protein 90 (HSP90) inhibitor 17-AAG prevent Aβ-driven synapse loss and memory deficits *in vivo*, likely by pre- and post-synaptic proteins upregulation, hence strengthening the existing synapses [226]. Interestingly, Resveratrol, a Sirtuin 1 activator, protects rats exposed to oligomeric Aβ from displaying disturbed memory acquisition and LTP induction [227]. These effects are probably mediated by neurogenesis and blockade of microglial and astrocytic activation, substantially reducing neuroinflammation [228, 229]. These two Resveratrol effects combined could contribute to increase neuronal and synaptic number in AD patients' brains, while also dampening the neurotoxic effects mediated by reactive glial cells. Thus, this drug comprises one of the most promising candidates for AD treatment in the near future. Finally, clinical trials using intranasal insulin applications have been successful in ameliorating cognitive functions of patients exhibiting mild to moderate AD [230]. Insulin works by preventing Aβ-derived diffusible ligands binding to neuronal surface, resulting in significant diminished spine loss [231]. It is worth mentioning that this strategy is currently under Phase II/III clinical trials (ClinicalTrials.gov Identifier: NCT01767909).

2.2. Multiple Sclerosis

Multiple Sclerosis (MS) is one of the most frequent demyelinating CNS disorders, affecting around 3 million people worldwide [232]. Patients bearing this neurological disorder often present motor, cognitive, visual and sensory deficits throughout the course of the disease, which worsens with aging [233-237]. These symptoms are widely viewed as the result of extensive white matter demyelination, associated with blood-brain barrier disruption, leading to massive inflammatory infiltration, followed by astrogliosis and microgliosis, neuronal injury, extensive excitotoxicity and neuroinflammation [233, 234, 238-242].

Even though most researchers have focused on the inflammatory aspects concerning white matter demyelination and its associated lesions, gray matter alterations have been regarded as an important aspect in MS, especially concerning the development of cognitive deficits [241]. For instance, it has been shown that decreased cognitive processing is associated with cortical lesions and atrophy in several brain regions [243], including the basal ganglia [244], thalamus [244, 245], sensorimotor, entorhinal and cingulate cortices [246], cerebellum [247], amygdala [248] and hippocampus [249, 250]. One of the mechanisms responsible for this phenotype is the extensive neuronal and glial cell loss present in the MS lesions and the extensive demyelination of cortical structures [250-253]. As such, several studies have identified that proinflammatory cascades, induced by both peripheric and activated CNS resident immune cells, are associated

with augmented apoptosis in MS patients and in the Experimental Autoimmune Encephalomyelitis (EAE) mouse model [252-256]. Thus, TNF-α has been found to induce oligodendrocytes programmed cell death in a caspase-independent fashion [254]. Moreover, Interferon γ (IFN-γ) promotes the cell death of oligodendrocytes and also of microglial cells, contributing to the reduction in myelination and gray matter volume observed in MS patients [255, 256]. In addition, IL-1β and glutamatergic excitotoxicity have also been demonstrated to activate apoptosis, triggering neuronal cell death *via* the p53 cascade [257], while augmented oxidative stress, due to increased reactive oxygen species production, is also implied to take part in the cell loss that takes place in MS [258]. Furthermore, the classical complement cascade plays a significant role in the induction of apoptosis of neuronal cells in MS. In fact, early reports have provided evidence that animals lacking the complement component C3 in an EAE model have milder disease phenotypes compared to their WT littermates, including decreased demyelination and diminished number of infiltrated macrophages and T cells [259]. Subsequent studies not only corroborate this data [260, 261], but also indicate the involvement of C5 in mediating cell death in an acute EAE model [262]. Additionally, recent findings obtained by Watkins *et al* [263] have shown increased C1q, C3b and C9 expression in the gray matter lesions in the cortex. These authors have also found elevated levels of microglial cells positive for the complement receptors CR3, C3aR and C5aR. Altogether, these data strongly suggest the formation of the membrane attack complex in the CNS cells of MS patients, leading to their death by apoptosis.

2.2.1. Synaptic Elimination might be Central for the Cognitive Decline During MS Progression

Synaptic elimination is an important neurodegenerative process that appears to take place in the CNS parenchyma of MS individuals and to lead to extensive the cognitive decline. As such, *post-mortem* analysis of MS patients and EAE mouse models have provided evidence for decreased synapse number in the hippocampus, insular, frontotemporal and occipital cortices, and striatum [250, 264-267]. In addition, the staining intensities for synapsin I, synaptophysin and PSD-95 are also reduced in the hippocampus of MS patients and in EAE mice [266, 267]. Even though these results and the involvement of the classical complement cascade in MS could suggest increased synaptic pruning, direct evidence for such a phenomenon in MS is sparse. Indeed, Machalidou and colleagues [268] have found increased C1q and C3d immunoreactivity in all hippocampal regions in the brain of MS patients. Also, they have demonstrated that these two complement factors colocalize with synaptophysin, both in neuronal synapses and inside activated microglia, indicating these cells are engulfing complement targeted synapses. These data suggest that synaptic pruning contributes to the diminished synapse density observed in MS patients. Conversely, CD47, which acts as a "don't-eat-me" signal, preventing phagocytosis of synapses by microglia, is downregulated in chronic MS lesions [269, 270]. Intriguingly, when CD47 is deleted in an EAE mouse model, the disease fails to develop to its full extent [270]. In contrast, when this molecule is blocked during the disease

course, it worsens EAE development in treated animals, on which it is possible to observe increased myelin phagocytosis by murine macrophages [270]. Although these studies did not access CD47 role in synaptic pruning, its downregulation during MS progression could prompt both activated microglia and infiltrating macrophages to excessively prune synapses due to inefficient recognition of this protective signal.

On the other hand, Freria *et al*. [271], upon analyzing spinal cord synapses, found that increased MHC-I expression in both astrocytes and microglia correlates with decreased immunostaining for synaptophysin, suggesting that MHC-I levels are inversely related to synaptic density. Genetic studies indicated that a cohort of MS patients possesses higher frequency of two progranulin alleles (rs9897526 A and rs5848 T) that are associated with increased disease severity and decreased progranulin expression levels [272]. In marked contrast, Vercellino *et al* [273] have provided evidence for strong expression of progranulin in activated microglia, macrophages and neurons around cortical lesions in MS patients. Moreover, they also show higher CSF progranulin levels in patients displaying the progressive form of the disease, compared to those in clinical remission. Adding more confusion to the role played by progranulin in MS, De Riz and colleagues [274] have argued that this factor does not play a significant role in this disease since they have found its CSF levels to be more correlated with aging than with MS *per se*. Despite progranulin importance in synaptic elimination, there is a lack of substantial evidence for the participation of progranulin in MS synapse loss, especially because only a few studies have aimed at investigating its role in this disease. In addition, previous reports indicate increased brain, CSF and serum levels of CX3CL1 in MS patients compared to healthy individuals [275, 276]. Since CX3CL1 expression in astrocytes does not differ between MS patients and controls [277], it is possible that increased CSF levels of this chemokine could come, at least in part, from neuronal origin or increased release of soluble CX3CL1 from the astrocytic plasma membrane. Furthermore, data points out that CX3CL1 expression in the brain is regulated by adenosine signaling and that blocking CX3CL1 impairs EAE development, especially dampening lymphocytes migration into the brain parenchyma [278]. Also, CX3CR1 deletion markedly decreases Natural Killer cell influx into the brain in EAE [278]. It is also worth mentioning that neuronal pentraxin receptor (NPR) is upregulated in MS patients, which might indicate that neuronal pentraxins are somehow involved in this disease progression [279]. However, whether these immune molecules are implicated in the enhanced synaptic elimination observed in MS patients is still unknown. Even though these data do not conclusively point to a direct association between increased synaptic elimination and disease progression, the altered levels of the aforementioned molecules in MS might indicate this could be the case.

Regarding deficient synaptogenesis, a phenomenon that could also explain the observed reduction in synaptic staining intensities in MS patients and EAE mouse models, little is known. Indeed, one of the fewest evidences pointing in this direction indicates a negative correlation between synapse number and paralysis severity in an EAE mouse model

[280]. In this study, proinflammatory cytokines released by T cells have been shown to either augment the production of secreted protein acidic and rich in cysteine (SPARC) or inhibit SPARC-like 1 (SPARCL1) synthesis. While SPARCL1 promotes the formation of excitatory synapses, SPARC blocks it [280]. Albeit this data provides support for disrupted synaptogenesis, the lack of evidence limits any further conclusion concerning the importance of this phenomenon in MS progression. Altogether, future research should be conducted to understand better to what extent increased synaptic pruning or decreased synaptogenesis could influence MS development.

Despite the scarcity of data regarding the molecular mechanisms involved in spine loss in MS, it is well known that glutamatergic and GABAergic transmissions are altered in this disease, especially in the case of the first system, which is implicated in triggering excitotoxic neuronal damage [239, 266, 281-283]. Elevated TNF-α level is observed during MS progression, leading to substantial increase in spontaneous excitatory post-synaptic currents (sEPSCs) and subsequent neuronal damage due to augmented glutamate release [240]. This elevated level of glutamate seems to be largely due to increased TNF-α release by astrocytes and microglia, ultimately leading to impaired memory in EAE and increased neurotoxicity [283, 284]. In addition, this cytokine also mediates increased synaptic turnover, even before microglial activation and lymphocyte infiltration in EAE mouse brains, suggesting that this proinflammatory molecule might also play an important role in modulating synapse density in MS [285]. Interestingly, treating EAE mice with the cannabinoid receptors 1 and 2 (CB1 and CB2, respectively) agonist WIN55,512-2 significantly ameliorates disease progression, even reducing cellular infiltrates in the spinal cord [286]. This effect is largely mediated by CB1, triggering subsequent downregulation of TNF-α levels, which, in turn, diminishes the glutamatergic excitotoxicity [286, 287]. Similar results are observed when microglial cells are treated with either the gap junction blocker carbenoxolone or the glutaminase inhibitor 6-diazo-5-oxo-L-norleucine, with both drugs preventing the excessive glutamate release [288]. Thereby, therapeutic strategies aiming at reducing either TNF-α or released glutamate levels comprise an attractive approach to ameliorate MS progression.

2.3. Schizophrenia

SCZ is a neurodevelopmental disorder that is characterized by high level of synapse elimination. This disorder is estimated to affect approximately 1% of the entire world population and its symptoms begin to manifest at late adolescence and early adulthood [289-290]. SCZ symptoms are often divided into three categories: positive symptoms (hallucinations, delusions, thought disorder and psychosis), negative symptoms (avolition, depression, anhedonia and loss of social drive) and cognitive deficits (disorganized speech, thought and attention deficits) [290, 291]. Anatomical studies using imaging techniques, such as magnetic resonance imaging (MRI), have identified several brain alterations in schizophrenic individuals. Thus, researchers have found substantial enlargements of the third and lateral ventricles, which are correlated with augmented cognitive deficits [292-295]. In addition, it is also perceived a 3% and 5.5-6.5% reduction in the whole cerebrum and hippocampal volume, respectively, as well as overall reduced cortical thickness [294-296]. Interestingly, this reduction in brain volume is not accompanied by the corresponding decrease in neuronal numbers. In fact, studies suggest that not only are neuronal numbers similar between schizophrenic and healthy individuals, but they might also be increased in the former group, especially in the pre-frontal cortex, a region implicated in SCZ [297-299].

Based on these findings, researchers hypothesize that SCZ brain volume and cortical thickness reductions are caused by altered morphological features in the neuropil [300]. *Post-mortem* tissue analyses have shown substantially decreased number of dendritic spines in several cortical structures, including the striatum, the subiculum and the temporal, auditory and pre-frontal cortices [300-305]. These evidences provide strong support for the hypothesis firstly proposed by Feinberg in 1983, that SCZ could arise from excessive synaptic pruning during adolescence. This phenomenon could lead to significant cortical connectivity alterations in the adulthood, and, ultimately, to the characteristic symptoms observed throughout disease progression [306]. Despite almost four decades after being proposed, the mechanisms whereby elevated synaptic elimination could account for the onset of SCZ are still poorly understood.

Even though schizophrenia etiology is still mostly unknown, several genetic and environmental risk factors are thought to trigger this neurodevelopmental disorder [289, 307]. Notably, genetic studies have provided the majority of evidences linking SCZ and abnormal synaptic pruning. For instance, Sekar and colleagues [308] have demonstrated that schizophrenic individuals possess genetic structural variants favoring the greater expression of C4A mRNA, one of the C4 isoforms found in the human genome. C4 activates C3 in the classical complement cascade and these authors have demonstrated that mice lacking C4 show abnormal eye-specific segregation in the dLGN as well as reduced C3-puncta colocalization at synapses [308]. Corroborating C4 involvement in SCZ, Prasad *et al* [309] have identified that both C4 isoforms (C4A and C4B) expression correlates with neuropil contraction in SCZ patients. Furthermore, chronic schizophrenic patients display higher blood levels of C4, while those at high-risk of developing psychosis present increased levels of both C3 and C4 compared to healthy individuals [310]. On the other hand, SIRPα, the CD47 receptor, is downregulated in the dorsolateral pre-frontal cortex of schizophrenic individuals [311]. These findings are particularly remarkable, as C4 is a pruning-promoting molecule, while SIRPα takes part in the protective signaling preventing synaptic elimination. Additionally, if brain complement component levels are actually elevated in SCZ, it is possible to speculate the involvement of mGluR1 in this phenomenon, similarly to what has been observed in Alzheimer's disease [207]. As such, augmented levels of mGluR1 has been observed in the pre-frontal cortex of SCZ patients [312], while non-synonymous mutations in the mGluR1 gene (*GRM1*) has been found in a cohort of schizophrenic individuals [313]. Moreover, the downstream target of mGluR1 activation, FMRP, is decreased in the blood of SCZ individuals [314]. Since C1q mRNA is repressed upon FMRP binding, these data might suggest a connection between

mGluR1 activation, which could also lead to LTD induction, and increased complement-dependent synaptic pruning in SCZ. In remarkable contrast, other genetic studies, using distinct schizophrenic patient cohorts, failed to detect the association between the classical complement cascade and schizophrenia [315-317]. This contradiction might reflect the high heterogenicity found between schizophrenic patients and the polygenic nature of this disorder. Therefore, further functional studies, using novel strategies, should be carried out to elucidate the actual contribution of the complement cascade to SCZ development.

Bergon and colleagues [318] have performed a large meta-analysis based on gene expression alterations found in schizophrenic individuals compared to healthy ones in order to find other suitable candidates important for synaptic elimination. Intriguingly, it has been shown that CX3CR1 is downregulated in both the brain and blood in SCZ patients. Moreover, another study identified that the genetic variant coding for $CX3CR1^{A55T}$ is associated with SCZ [319]. The functional validation of this mutated CX3CR1 form *in vitro* indicated that it leads to impairments in downstream signaling upon CX3CL1 binding, which might affect the microglial phenotype in this disorder. Additionally, it is important to mention that common genetic variant analyses indicate that polymorphisms in the MHC locus are significantly associated with SCZ [320, 321]. Another genetic study has identified progranulin genetic variants conferring higher risk for schizophrenia [322], whereas others found that glypicans, which are responsible for neuronal pentraxin release regulation [323], are also related to this disease [324].

Post-mortem analyses and imaging techniques point to the activation of microglial cells in SCZ [324-326]. This microglial phenotype suggests the occurrence of neuroinflammation and enhanced levels of proinflammatory molecules in the brain of schizophrenic individuals [327-328]. For instance, evidences indicate elevated TNF-α and IL-6 in the brain, blood and CSF of SCZ patients [328-331]. On the other hand, increased IL-1β levels, a classic proinflammatory cytokine, have been implicated in SCZ, although these results are disputable [330-332]. Nonetheless, whether these cytokines contribute to promote microglia-mediated synaptic pruning in schizophrenia is still unknown. In an attempt to identify whether this is the case, studies using animals to model environmental factors have been used. Indeed, using the maternal immune activation model, which mimics prenatal infection as a risk factor in SCZ [333], Mattei and colleagues [334] have verified that the microglia of the offspring display an activated phenotype with transcriptomic profile and cytokine expression partially matching those found in SCZ patients. Surprisingly, synaptic density in these animals is also reduced [335]. Unfortunately, the behavioral alterations observed in these animals recapitulate those associated with autism and not schizophrenia [336]. In addition, another major drawback of using this kind of model is the absence of the genetic component of SCZ, which does not allow the execution of studies aiming at analyzing the interaction between genetic and environmental risk factor.

The use of iPSCs derived from schizophrenic individuals could partially solve this issue, at least for studies attempting to investigate major changes at the molecular and cellular levels. Indeed, Brennand and colleagues [337] have found that iPSC-differentiated neurons derived from SCZ patients exhibit reduced neuronal connectivity and neurite numbers and decreased expression of PSD95 and glutamate ionotropic receptor kainate 1 expression. Additionally, Sellgren *et al* [338] have shown that microglial-like cells derived from schizophrenic individuals display a higher phagocytic index of synaptosomes obtained from hiPSC-derived neuronal preparations. These data indicate increased synaptic engulfment capacity by microglia in SCZ, which could underpin the elevated synapse loss observed in this condition. Interestingly, this higher phagocytic capacity of SCZ microglial-cells is inhibited by minocycline treatment, a drug recently suggested for schizophrenia treatment [338, 339].

CONCLUSION

In recent years, several lines of evidence have indicated a prominent role of synaptic elimination as a key component in modulating neuroplasticity in the CNS. Nonetheless, disturbances in this process are likely underpinning the cognitive deficits often observed in many of the most relevant neurological disorders afflicting humankind. In this review, we summarized the most up-to-date information available in the scientific literature, regarding what is currently known about synaptic pruning in AD, MS and SCZ, three of the most relevant neurological disorders. Nevertheless, there is still much to be learned about this process, especially concerning the involvement of immune molecules and glial cells in mediating synapse maintenance/elimination in these disorders.

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