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Review

Excitatory-inhibitory imbalance in Alzheimer's disease and therapeutic significance

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A B S T R A C T

The interplay between excitatory and inhibitory circuits underlies the brain's processes and their dysregulation has been linked to cognitive decline, psychiatric disorders and epilepsy. In patients with Alzheimer's disease (AD), an elevated occurrence of seizures has been observed in both sporadic and familial forms of the condition. Although seizure activity in AD has been mainly viewed as a result of neuronal cell loss and considered to occur in later stages, it is now becoming increasingly clear that aberrant neuronal activity may be more common in patients at earlier stages than previously thought and may trigger and contribute significantly to cognitive defects. Here, we review alterations of inhibitory and excitatory circuits that may lead to overexcitability and early dysregulation of neuronal networks in the context of AD and therapeutic outcomes of restoring excitatory/inhibitory balance.

1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by declarative memory impairments and increasingly severe cognitive decline leading to dementia. To date, no successful treatment has been found. AD pathology is predominantly characterized by the occurrence of amyloid beta (Ab) plaques in the brain, neurofibrillary tangles of hyperphosphorylated tau, as well as neuronal loss. While Ab and tau may drive AD progression, the pathogenic cascade that leads to AD appears to start decades before these clinical symptoms are present. In particular, subjects at genetic risk for AD show hippocampal hyperactivity (as measured with fMRI) during memory tasks (Bookheimer et al., 2000; Dickerson et al., 2005; Quiroz et al., 2010) and impaired default network activity (Filippini et al., 2009), indicating the presence of early network alterations. Importantly although AD pathology is related to global measures of cognition in unimpaired elderly subjects (Bennett et al., 2012), some individuals display Ab accumulation without dementia (Bennett et al., 2012; Lue et al., 1996; Roberts et al., 2018; SantaCruz et al., 2011). In fact, despite amyloid plaques being a hallmark of the disease, the density of Ab deposits does not significantly correlate with AD progression (Arriagada et al., 1992; Berg et al., 1993; Bierer et al., 1995; Dickson et al., 1992; Guillozet et al., 2003; Schmitt et al., 2000), or does not correlate as well as other measurements such as synaptic loss, which is regarded as the best predictor (Bennett et al., 2004; Blennow et al., 1996; Giannakopoulos et al., 2003; Lue et al., 1996; Scheff and Price, 1993; Terry et al., 1991). There is growing evidence that alterations of the amyloid precursor protein (APP) and particular isoforms of soluble Ab peptides can alter synaptic function and affect cognition before any neurodegeneration or plaque deposition is observed in the brain (Balducci et al., 2010; D'Hooge et al., 1996; Giacchino et al., 2000; Mucke et al., 1994, 2000; Oddo et al., 2003; Shankar et al., 2008).

Beyond the main pathological hallmarks of AD, synaptic dysfunction is also of major importance and AD has consequently been referred to as a "disease of synaptic failure" (Selkoe, 2002). Particularly, changes in excitatory and inhibitory synapses releasing glutamate and GABA, respectively, have gathered increasing interest as a mechanism contributing to AD pathology. The fine balance between excitatory and inhibitory transmission (E/I balance) is essential for brain oscillations (Amilhon et al., 2015; Boyce et al., 2016; Huh et al., 2016) and normal cognitive function (Zhou and Yu, 2018). Perturbations in E/I balance probably contribute to cognitive changes in AD (Busche and Konnerth, 2016; Selten et al., 2018), considering abnormal oscillatory rhythmic activity and network hypersynchrony are observed in AD mice models and AD patients (de Waal et al., 2012; Goutagny et al., 2013; Irizarry et al., 2012; Lozsadi and Larner, 2006; Osipova et al., 2005; Palop et al., 2007; Palop and Mucke, 2016; Vogt et al., 2011).

2. Abnormal network activity in AD promotes epileptiform activity

Significant E/I imbalance likely contributes to AD pathogenesis

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since up to 22% of patients experience unprovoked seizures, with rates increasing up to 58% in familial forms of AD (Amatniek et al., 2006; Friedman et al., 2012; Larner, 2011; Mendez and Lim, 2003; Vossel et al., 2013, 2016). Seizures in AD can be convulsive tonic-clonic, or more prevalently non-convulsive with patients experiencing altered consciousness, amnestic periods, and confusion which can go undiagnosed for years (Vossel et al., 2013). Furthermore, at least 20% of patients with AD experience transient episodes of amnestic wandering and disorientation, common elements of several dementias, which have been associated with epileptiform discharges (Bradshaw et al., 2004; Lee et al., 2012; Rabinowicz et al., 2000). It is likely that epileptiform activity in the early stages of AD is often underdiagnosed and undetectable as intracranial electrodes positioned adjacent to the mesial temporal lobe may be necessary to reveal abnormal electrical signals such as spike and wave activity during sleep in patients with no history of epilepsy (Brown et al., 2018; Lam et al., 2017).

There is a large number of studies suggesting that increases in Ab, and particularly early soluble forms of Ab such as oligomers, as well as Ab associated proteins, are key factors responsible for altering E/I balance. Such rapid increases in soluble forms of Ab are central to familial early onset forms of AD which have mutations in the gene for APP or presenilin-1 (PSEN1) (Brouwers et al., 2008; Potter et al., 2013; Shepherd et al., 2009; Suzuki et al., 1994). In AD transgenic mouse models with similar APP mutations, prominent neuronal hyperactivity and impaired E/I are also observed. For example, amyloid oligomers in APP mice models were shown to acutely affect synaptic transmission (Busche et al., 2012) and change the structure of the circuit (i.e. dendritic morphology) that directly cause hyperexcitability (Šišková et al., 2014). Mice with overexpression of mutated APP, or mutated PSEN1 or ApoE4 genes (a risk factor firmly linked to sporadic AD in humans), display spontaneous seizures and spike-wave discharges (SWDs), suggesting an early E/I imbalance linked to amyloid (Born, 2015; Born et al., 2014; Minkeviciene et al., 2009; Nuriel et al., 2017). SWDs are of particular interest as an early feature of E/I imbalance in AD, as they occur even before the presence of spontaneous seizures (Bezzina et al., 2015; Born et al., 2014; Kam et al., 2016; Nygaard et al., 2015; Verret et al., 2012). SWDs reflect sudden, transient synchronous hyperactivity, consisting of high voltage deflections with amplitudes exceeding twice the baseline of recording, and resemble the waveform of interictal spikes (Bezzina et al., 2015; Kam et al., 2016). Recent studies have focused on these SWDs in AD mouse models as an important early factor (as illustrated in Fig. 1) underlying or contributing to cognitive defects, and are a relevant marker in the diagnosis of epilepsy (Krendl et al., 2008; Rosati et al., 2003; Staley et al., 2011). SWDs are notable in AD models carrying the APP Swedish mutation, which increases overall Ab levels, in conjunction with other mutations, including the J20 (Palop et al., 2007), Tg2576 (Bezzina et al., 2015), APP/TTA (Born et al., 2014), APP/PS1 (PSEN1) (Minkeviciene et al., 2009; Reyes-Marin and Nuñez, 2017), and 3xTg (Nygaard et al., 2015) models. To study the role of APP in the incidence of SWDs, models that enable the expression of the human-mutated APP at different time points in a tetracycline-responsive manner with the use of tetracycline analogs have been created (called APP/TTA model, where TTA stands for tetracycline-controlled transactivator protein). Once APP is expressed, SWDs are observed from the earliest time point the authors examined, and their number is higher during the light cycle when sleep is more frequent (Born et al., 2014). The occurrence of SWDs was analyzed in more detail by Kam et al. (2016) in Tg2576 mice, and SWDs were found to appear before plaque deposition, were more prominent in quiet wakefulness and sleep, and especially during rapid eye movement sleep (REM). A similar distribution of SWDs during sleep has also been observed in the J20 model before widespread plaque deposition (Brown et al., 2018). On the other hand, Brown et al. also measured the incidence of interictal spikes in a patient with amnesic mild cognitive impairment using in-depth electrodes, and found a higher incidence of events during non-REM rather than REM sleep. This is in agreement with studies of temporal lobe epilepsy, where the rate of interictal spikes is generally higher during non-REM sleep (Clemens et al., 2003; Lieb et al., 1980; Rossi et al., 1984; Sammaritano et al., 1991). The discrepancy with AD animal studies may be partially dependent on the recording area, since there is evidence that the prevalence of interictal spikes is higher during REM sleep if recording from the primary epileptogenic region in patients with epilepsy (Lieb et al., 1980; Rossi et al., 1984; Sammaritano et al., 1991). Nevertheless, the occurrence of SWDs during sleep and quiet wakefulness may have significant implications for memory impairment since these periods are known to be necessary for memory consolidation (Boyce et al., 2016; Buzsáki, 2015; Girardeau et al., 2009; Karlsson and Frank, 2009).

Although not as much is known regarding the incidence of seizures in tau models without APP mutations, aggregates of tau have been reported in patient with epilepsy (Tai et al., 2016) and reducing tau in experimental models of epilepsy ameliorates seizures (Holth et al., 2013). FTDP-17 mice (a model of frontotemporal dementia with parkinsonism linked to chromosome 17 which overexpresses human mutant tau) have spontaneous seizures starting as early as 5 months of age, before tau aggregates are present (García-Cabrero et al., 2013). Tau also appears to modulate hyperactivity and seizure incidence in rodents, as knocking out tau completely, or reducing tau levels in APP models, reduces SWDs and prevents increased susceptibility to induced seizures (Roberson et al., 2007, 2011).

3. Excitatory disruption and hyperactivity

In AD, there has been a strong focus on excitatory dysfunction as the basis for E/I disruption. Typically, it has been suggested that changes in excitatory synaptic transmission have a key role in the aberrant hyperactivation and hypersynchrony of circuits resulting in the generation and spreading of epileptic discharges. Similarly, administration of soluble Ab in vivo (Busche et al., 2012), in vitro (Minkeviciene et al., 2009) and in neuronal cultures (Cuevas et al., 2011) have also been shown to generate hyperexcitability in hippocampal neurons and circuits. The Ab-mediated increase in neuronal excitability could be due to several mechanisms associated with glutamate synaptic transmission. Ab soluble oligomers are known to rapidly enhance hippocampal NMDAR currents in vitro (Wu et al., 1995), in vivo (Molnár et al., 2004) and in cell membranes of AD patients microtransplanted into oocytes

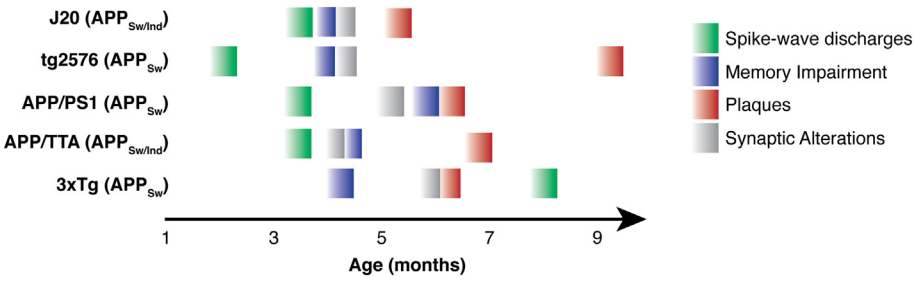

Fig. 1. Earliest recorded Spike Wave Discharges (SWDs) in AD models. The corresponding APP mutation is in parenthesis. References: J20 (Mucke et al., 2000; Palop et al., 2007; Sanchez et al., 2012; Verret et al., 2012). Tg2576 (Jacobsen et al., 2006; Kam et al., 2016; Kawarabayashi et al., 2001). APP/PS1 (Minkeviciene et al., 2009; Reyes-Marin and Nuñez, 2017; Schmid et al., 2016; Trinchese et al., 2004). APP/TTA: (Born et al., 2014; Marin et al., 2016; Sri et al., 2019). 3xTg: 8 to 10 months is the only time point were SWDs have been studied in this model to date (Billings et al., 2005; Nygaard et al., 2015; Oddo et al., 2003).

(Texidó et al., 2011), which may all directly cause increases in neuronal firing.

Moreover, soluble Ab oligomers could cause hyperexcitability by disrupting glutamate uptake as demonstrated by experiments employing cultured neurons and astrocytes, where Ab directly alters glutamate transporter expression and/or function (Fernández-Tomé et al., 2004; Harris et al., 1996; Matos et al., 2012). The disruption of glutamate transporters, named excitatory amino acid transporters or EAATs, can cause abnormal increases in extracellular glutamate concentrations triggering elevated spontaneous excitatory postsynaptic currents, population spike frequencies, and impairments in long-term potentiation (Lei et al., 2016; Li et al., 2009b). In addition, reducing glutamate transporters can have significant effects on excitability because these transporters can normally prevent the generation and spread of seizures (Demarque et al., 2004). Glutamate is also a GABA precursor, consequently disruption of glutamate reuptake could indirectly reduce GABAergic synthesis, intensifying E/I imbalance and further promoting hyperexcitability (Sepkuty et al., 2012). Such reductions in glutamate transporter expression have been reported in AD patients and may contribute to reductions in glutamate uptake, E/I imbalance and neurodegeneration (Masliah et al., 1996; Scott et al., 2011).

Additionally, APP and soluble Ab can modulate synaptic plasticity and glutamate receptor trafficking (see Hoe et al., 2012 for review). APP levels have been shown to change early during development and peak in the second post-natal week, which coincides with the NMDAR developmental receptor subtype switch from GluN2B to N2A (Liu et al., 2004; Löffler and Huber, 1992). However, if APP is over-expressed, this can cause an upregulation of NMDARs containing GluN2B subunits in the hippocampus due to increased GluN2B mRNA levels (Cousins et al., 2009; Hoe et al., 2009). This increase in GluN2B NMDA receptor subtype may in turn increase excitability and directly contribute to seizures (Chen et al., 2016; Okuda et al., 2017). Although the mediator behind this APP synaptic regulation may involve its intracellular domain (Pousinha et al., 2017), the oligomeric form of Ab can alter surface levels of GluN2B NMDARs and this is required for the seizure phenotype to be present in the APP/PS1 AD mice model (Um et al., 2012). At the same time, Ab also disrupts the ability of other mechanisms to limit excessive NMDAR activity, thus adding to network hyperexcitability (You et al., 2012).

Apart from its role in modulating receptor trafficking, soluble Ab can directly activate the GLuN2B NMDA receptor subunit, thereby disrupting intracellular calcium homeostasis and synaptic plasticity (Ferreira et al., 2012; Li et al., 2011). Overactivation of glutamate receptors has been shown to be highly toxic, an effect termed excitotoxicity. Undesired increases of intracellular Na^+ and Ca^{2+} that result in cell death will occur once the NMDAR Mg^{2+} block is released by the persistent depolarization of the cell (Arundine and Tymianski, 2003; Choi, 1985; Koh and Choi, 1991; Liu et al., 2007; Rothman, 1985). A substantial body of evidence indicates that this neurotoxic mechanism may contribute to the eventual neuronal loss seen in AD (Brorson et al., 1995; Hynd et al., 2004; Mattson et al., 1992; Mattson and Goodman, 1995; Miguel-Hidalgo et al., 2002; Tominaga-Yoshino et al., 2001; Yatin et al., 2001). Moreover, activation of NMDARs is also known to regulate APP trafficking and processing, as well as facilitating Ab production (Bordji et al., 2010; Lesné et al., 2005; Hoe et al., 2009), in turn potentially creating a feedback loop which would eventually result in cell death.

Ab toxicity may also be potentiated by tau through increases in glutamatergic signalling leading to excitotoxicity. Tau can stabilize NMDARs in synapses and increase NMDA receptor-dependent currents through an aberrant association with Fyn, ultimately strengthening glutamate neurotransmission (Ittner et al., 2010). Notably, the reduction of tau is able to supress NMDA dependent excitotoxicity in hippocampal slices (Miyamoto et al., 2017) and decrease hyperexcitability in the form of SWDs and seizure activity in animal models as noted previously (AD: Roberson et al., 2007; Epilepsy: Holth et al., 2013). This enhanced glutamatergic signalling has been proposed to account for the higher NMDAR binding found in post-mortem brain tissue from AD patients (Ułas et al., 1994).

Finally, Ab can also interact with mGluRs, and its oligomeric form in particular is able to aberrantly cluster mGluR5, which in turn elevates intracellular calcium and could ultimately cause synaptic deterioration (Renner et al., 2010). In agreement with this, patients with AD have enhanced mGluR5 levels as measured by immunostaining in comparison to age-matched controls, at least in astrocytes (Casley et al., 2009) and deletion of mGluR5 is known to improve cognitive decline in the APP/PS1 model of AD (Hamilton et al., 2014).

Excitatory circuitry alterations may also directly dysregulate inhibitory neurotransmission. There is evidence that glutamate may developmentally regulate axons and dendrites of GABAergic interneurons (De Marco García et al., 2011), and that glutamatergic signalling itself is capable of modulating post-synaptic $GABA_A$ receptor expression and clustering (Bannai et al., 2015) as well as inhibitory circuit plasticity (Mapelli et al., 2016; McLean et al., 1996; Moreau and Kullmann, 2013). Although there is a great deal of data indicating that aberrant changes in excitatory synaptic transmission are important for AD progression, there is significant evidence suggesting that disruption in GABAergic synaptic transmission is also important.

4. Inhibitory disruption

Although the predominant view has been that inhibitory synaptic transmission is relatively more resilient in AD (Francis et al., 1993; Palmer and Gershon, 1990; Reinikainen et al., 1988; Rissman and Mobley, 2011), it is now becoming clear that inhibitory circuits are severely disrupted early in the disease process (Bell et al., 2006; Rossor et al., 1982; Ulrich, 2015), as depicted in Fig. 2. For example in the APP/TTA AD mice model, an E/I imbalance is apparent since administering 1.75 mg/kg of the $GABA_A$ antagonist picrotoxin leads to seizures within an hour in vivo, an effect not observed with the same dosage in controls (Born et al., 2014). Another $GABA_A$ receptor antagonist, Pentylenetrazol, has also been shown to induce seizures at a higher rate in the Tg2576 (Westmark et al., 2008), J20 (Palop et al., 2007) and tgCRND8 (Del Vecchio et al., 2004) AD models compared to controls. These effects may be explained by factors related to reduced inhibitory function. For instance, Ab application to cortical slices in vitro results in the endocytosis of $GABA_A$ receptors (Ulrich, 2015) and evidence from AD patients suggests that GABAergic receptors provide smaller inhibitory currents, indicating a remodeling of GABAergic inhibition in human AD (Limon et al., 2012). Other studies report that specific GABA receptor subunits are downregulated in particular regions (Howell et al., 2000; Limon et al., 2012; Mizukami et al., 1998; Rissman et al., 2003), while a preservation in the expression of other subunits has also been observed (Limon et al., 2012; Mizukami et al., 1997; Rissman et al., 2003), suggesting area specific changes in receptor composition (see Rissman and Mobley, 2011 for review).

Ab also produces a decrease in GABA release from fast-spiking interneurons innervating principal cells in slice (Ren et al., 2018). Fast spiking firing patterns have been associated with parvalbumin (PV) expressing GABAergic neurons since the 1980s (Kawaguchi et al., 1987; see Hu et al., 2014 for review), have been linked to memory consolidation (Ognjanovski et al., 2017; Xia et al., 2017) and are essential for spatial working memory (Murray et al., 2011). Stimulating PV interneurons, but not other cell types, can enhance gamma oscillatory activity (20-80 Hz) (Cardin et al., 2009) and increases in this frequency band during memory encoding have been linked with memory performance (Sederberg et al., 2006; Yamamoto et al., 2014). Early in the J20 AD model, a reduction of firing from PV interneurons has been observed in areas such as the hippocampus (Mondragón-Rodríguez et al., 2018) and linked to the loss of voltage gated sodium channel subunit Nav 1.1 leading to a decrease of GABAergic inhibition and possibly gamma power (Verret et al., 2012). Importantly, interneuron

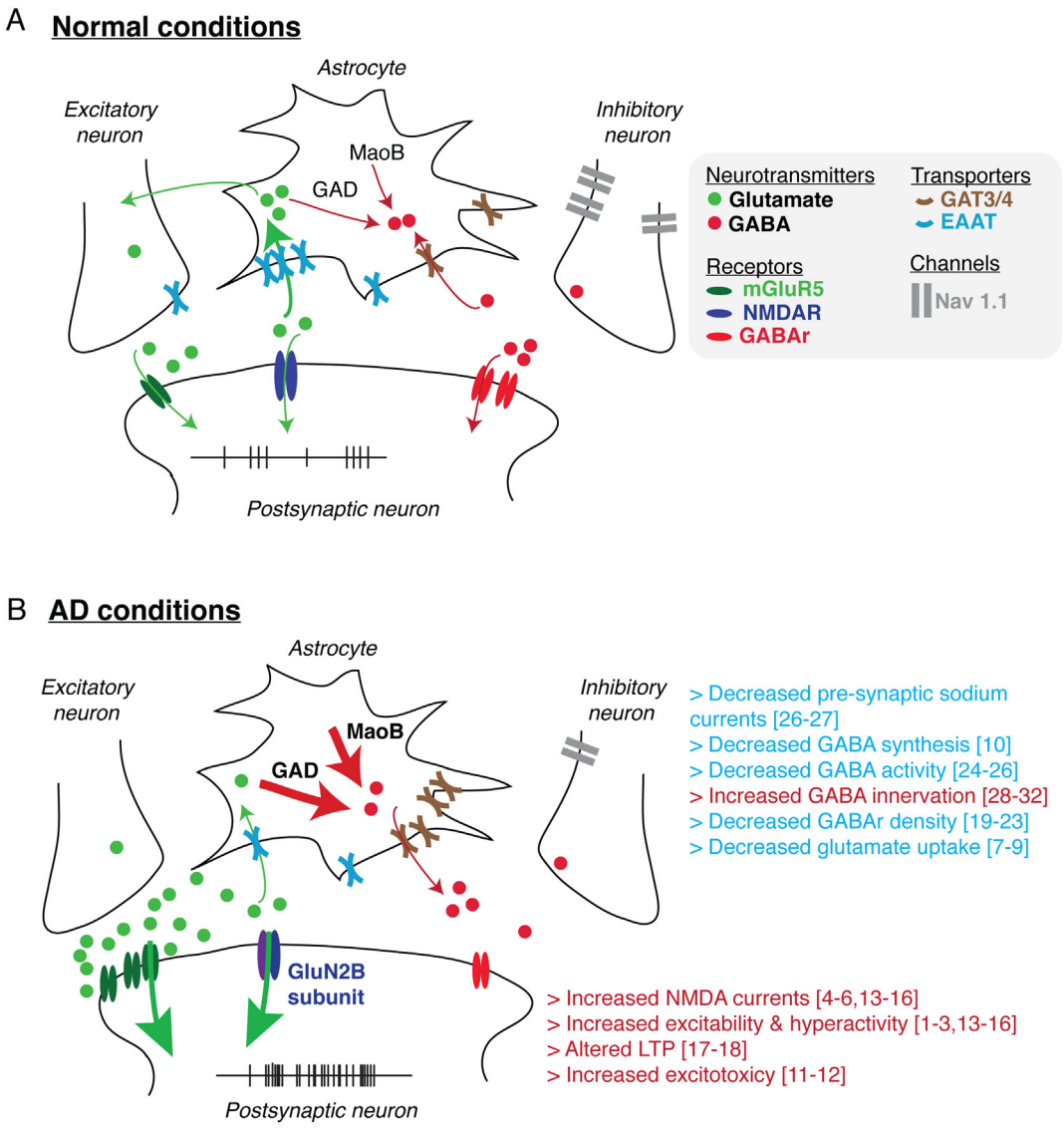

Fig. 2. Schematic of neural network in normal and AD conditions, including glutamatergic/GABAergic neurons and connections. Presynaptic glutamate release triggers postsynaptic activation through the binding of membrane receptors. In the synaptic cleft, glutamate can be taken up by transporters located in astrocytes and converted to glutamine and GABA. On the other hand, presynaptic GABA release triggers postsynaptic deactivation through GABAr, and can also be taken up by astrocytic GABAergic transporters. In AD conditions, glutamatergic concentration in the synaptic cleft is increased due to altered glutamatergic transport. This leads to overactivation of postsynaptic neurons through upregulated NMDA and mGluR receptors. GABAergic transmission is impaired due to a loss of presynaptic sodium currents and postsynaptic GABA receptors. To counteract hyperexcitability, astrocytes may facilitate GABAergic synthesis, release and innervation. [1] Busche et al., 2012. [2] Minkeviciene et al., 2009. [3] Cuevas et al., 2011. [4] Molnár et al., 2004. [5] Texidó et al., 2011. [6] Wu et al., 1995. [7] Fernández-Tomé et al., 2004. [8] Harris et al., 1996. [9] Matos et al., 2012. [10] Sepkuty et al., 2012. [11] Masliah et al., 1996. [12] Scott et al., 2011. [13] Cousins et al., 2009. [14] Hoe et al., 2009. [15] Chen et al., 2016. [16] Okuda et al., 2017. [17] Ferreira et al., 2012. [18] Li et al., 2011. [19] Ulrich, 2015. [20] Howell et al., 2000. [21] Rissman et al., 2003. [22] Limon et al., 2012. [23] Mizukami et al., 1998. [24] Ren et al., 2018. [25] Mondragón-Rodríguez et al., 2018. [26] Verret et al., 2012. [27] Martinez-Losa et al., 2018. [28] Li et al., 2009a. [29] Bell et al., 2003. [30] Born et al., 2014. [31] Hollnagel et al., 2019. [32] Palop et al., 2007.

transplants overexpressing Nav1.1 in cortex and hippocampus were able to reduce hypersynchrony, enhance gamma oscillations and improve memory in the same transgenic mouse model (Martinez-Losa et al., 2018). Along the same line, stimulating PV interneurons at gamma frequency appears to decrease Ab-40 and 42 isoforms (Iaccarino et al., 2016). In findings linked to interneuron hypoactivity, neuronal pentraxin-2, a protein secreted by excitatory neurons which specifically mediates activity-dependent strengthening of excitatory synapses onto PV interneurons (Chang et al., 2010), is down-regulated in the brains of AD patients (Xiao et al., 2017).

Several lines of research also show that APP itself may modulate GABAergic inhibition and $GABA_A$ receptors (Chen et al., 2017; Seabrook et al., 1999; Yang et al., 2009). Most recently, Rice et al. (2019) demonstrated that secreted APP is able to bind to $GABA_B$ receptors to suppress synaptic vesicle release, thus modulating hippocampal synaptic plasticity. In addition to APP, the AD risk factor ApoE4 is known to decrease both the number of interneurons as well as GABAergic innervation in ApoE4 knockin mice (Li et al., 2009a) whereas conditionally deleting ApoE4 in neurons rescues GABAergic neuronal loss and memory deficits (Knoferle et al., 2014). Other studies point to important changes in synaptic inhibition and potential compensatory responses of the GABAergic circuitry that are associated with hyperactivity and cognitive decline in AD models. For instance, in transgenic lines where early epileptic discharges have been observed, an increase in the number of GABAergic presynaptic boutons and GABAergic terminals in cortex (Bell et al., 2003; Born et al., 2014), CA1-3

hippocampal regions (Hollnagel et al., 2019) and dentate gyrus (Palop et al., 2007) have been noted.

As the disease progresses and once amyloid deposits are present, the number of GABAergic presynaptic boutons is severely decreased near plaques in the cortex of APP/PS1 mice at 18 months of age (Bell et al., 2006). A diminishing number of GABAergic cortical terminals at the perisomatic level immediately adjacent to Ab plaques has also been observed in AD patients (Garcia-Marin et al., 2009; Hardy et al., 1987), as well as general lower levels of GABA neurotransmitters in temporal cortices (Gueli and Taibi, 2013; Seidl et al., 2001). In particular, somatostatin-expressing GABAergic hippocampal interneurons which are essential for learning and memory (Davies et al., 1980; Siwani et al., 2018), appear to be preferentially affected. In a very complete longitudinal study spanning the age of 4 to 11 months, Schmid et al. (2016) imaged this population in APP/PS1 mice in vivo, and found progressive axonal loss starting at 5 months of age and additional plasticity deficits after a learning task, dependent on plaque proximity. Related findings have been described in temporal lobe epilepsy models and patients (Dinocourt et al., 2003; Robbins et al., 1991), as well as in AD patients, where somatostatin-like immunoreactivity is reduced in cortex and hippocampus (Davies et al., 1980; Davis et al., 1999; Grouselle et al., 1998; Rossor et al., 1980).

Consistent with a reduction in GABAergic inhibition, a decreased number of GABAergic neurons in the hippocampus has also been found in the tgCRND8 (Krantic et al., 2012), APoE4 knockin (Li et al., 2009a) and 3xTg AD models (Zallo et al., 2018). Specially neuronal loss (50–60%) is markedly pronounced in the stratum oriens of CA1–3 and dentate regions of APP/PS1 mice, before any other neural loss is observed in this structure (Baglietto-Vargas et al., 2010; Ramos et al., 2006). In AD patients, a reduction of GABAergic neurons measured using GAD65 immunostaining has been noted in the dentate gyrus (Schwab et al., 2013) and region-specific hippocampal GABAergic morphological changes, and neural loss has been described in PV (Brady and Mufson, 1997) and somatostatin/NPY (Chan-Palay, 1987; Chan-Palay et al., 1986) interneuron populations. Other cell type changes were not compared in these hippocampal measurements, but in the entorhinal cortex, GABAergic interneuron degeneration precedes changes to principal cells, at least in the early stages of the disease (Mikkonen et al., 1999; Solodkin et al., 1996).

In addition to neurons, astrocytes modulate the brain's excitatory/inhibition balance, playing an important role in brain homeostasis (McKenna et al., 2002; Pekny et al., 2016; Rose and Ransom, 1996; Rothstein et al., 1996; Schousboe and Waagepetersen, 2003; White et al., 2002) and changes in their function appear early on in AD patients (Carter et al., 2012) and AD animal models (Heneka et al., 2005). For instance, as a response to glutamatergic stimulation, astrocytes can reverse the function of GABAergic GAT2/3 receptors in slice, increasing GABA release (Héja et al., 2009). This reversal has been shown to lead to an abnormal tonic inhibition in the 5xFAD mouse model, which can be countered by the application of GABA transporter inhibitors, supporting a dysregulation of GABAergic mechanisms (Wu et al., 2014). Indeed in this same model, the enzymes GAD65 and MaoB are upregulated and GABA synthesis is therefore enhanced in areas such as the dentate gyrus (Jo et al., 2014; Wu et al., 2014). Results from patients further corroborate the involvement of astrocytes in the early remodeling of the GABAergic system, as the largest signal of MaoB is detected in activated astrocytes in prodromal AD (Saura et al., 1994). The expression of astrocytic transporters in patients is clearly altered as well, but these changes are complex and region specific (Fuhrer et al., 2017). While GAT3, the human/rat equivalent of GAT4 in mice, has been found to be upregulated in the dentate gyrus (Wu et al., 2014), it is downregulated in other hippocampal and cortical areas (Fuhrer et al., 2017). In Fuhrer et al.'s study, GAT3 downregulation was accompanied by an increase of the astrocytic transporter BGT1, and a similar co-regulation between GAT3 and BGT1 has been described after excitatory injury of the hippocampus (Zhu and Ong, 2004) which the authors propose is a protective mechanism.

5. Targeting cognitive dysfunction by circuit modulation

Identifying the mechanisms that promote E/I dysfunction in early AD can guide the development of future therapies. To date, only four drugs have been approved to treat the symptoms of AD, and they can be separated in two categories: acetylcholinesterase inhibitors (AChEI) comprising Donepezil, Galantamine and Rivastigmine, and the NMDAR GluN2B antagonist Memantine. AChEI drugs increase cholinergic transmission and are recommended for the treatment of mild to moderate AD (Arce et al., 2009; Ballard, 2002; NICE, 2011). Memantine is the only NMDAR antagonist used by AD patients to prevent decline in cognition (although the effects are modest), and recommended for treatment of moderate to severe AD (Limapichat et al., 2013; Matsunaga et al., 2015; NICE, 2011). These drugs only temporarily reduce the rate of decline, but do not stop its progression.

Presently, treatments focusing on amyloid reduction and clearance have dominated the therapeutic landscape even though amyloid only weakly correlates with cognitive decline in the symptomatic phase of the disease. These drugs aim to clear pre-existing plaques or inhibit the formation of new ones by using monoclonal antibodies against Ab or by inhibiting the secretases that cleave APP producing the Ab isoforms forming plaques. However, it remains to be determined if eliminating or reducing Ab will have a significant effect on the cognitive decline in AD patients. A recent phase III clinical trial with the monoclonal antibody Solanezumab, reduced free Ab levels by at least 90%, but was unable to clear existing plaques or slow-down cognitive decline (Honig et al., 2018). Likewise, the beta-secretase inhibitor Verubecestat was shown to reduce Ab cerebrospinal fluid levels by 75%, but had no effect in decreasing the rate of cognitive decline (Egan et al., 2018). Similar results have been found in clinical trials with gamma secretase inhibitors (Doody et al., 2013) and although these and other anti-amyloid drugs have been proven ineffective (Biogen, 2019; Sevigny et al., 2016), clinical trials targeting different Ab molecules are still ongoing and may show promise (Salloway et al., 2014; see Folch et al., 2018 for review).

The overall lack of success of amyloid therapies suggest that once dementia is present, disease progression is likely independent of Ab production and could be irreversible. It is reasonable to assume that treatments targeting amyloid should be implemented early in the disease and not simply focus on plaque clearance, as the pathological cascade is thought to begin 10 to 20 years before the onset of clinical symptoms (Bateman et al., 2012; Villemagne et al., 2013). This highlights the need for developing useful biomarkers which may aid clinicians in the detection of the disease at earlier stages, and ease the recruiting of patients for clinical trials before the dementia stage has been reached (Blennow and Zetterberg, 2018).

Interventions targeting mechanisms reducing the E/I imbalance discussed in this review, may provide new therapeutic opportunities to improve cognition and quality of life in patients. For example, Memantine is one such drug that targets NMDAR GluN2B and can taper the rate of cognitive decline by directly regulating hyperexcitability. Other glutamate receptor antagonists such as Ifenprodil, a GluN2B selective antagonist, can prevent Ab induced $Ca2+$ rise, and synaptic plasticity impairments in vitro (Ferreira et al., 2012; Hu et al., 2009; Rönicke et al., 2011). mGluR5 antagonists show some promise when tested in models of AD since they can reduce Ab production, seizures, and help restore long-term potentiation (Kazim et al., 2017; Rammes et al., 2011). Overall, these results suggest the validity of developing drugs targeting the glutamatergic system as they may potentially provide beneficial effects to help restore E/I balance. Using a combination of glutamate receptor antagonists with other drugs in the treatment of AD is now being explored. One such combination is Memantine and AChEIs to potentially achieve additive positive effects in patients (Parsons et al., 2013; Tariot et al., 2004).

Anti epileptic drugs such as the closely related Brivaracetam and

Levetiracetam have been shown to successfully normalize the excitation/inhibition balance observed in AD mice models. Specifically, when J20 mice are treated with Levetiracetam, they show a reduction in epileptiform activity (such as SWDs), and an improvement in memory (Sanchez et al., 2012). Brivaracetam has also been successful at decreasing SWD hyperactivity in the APP/PS1 and 3xTg AD models while ameliorating spatial memory (Nygaard et al., 2015). Although their mode of action remains to be clearly established, Brivaracetam and Levetiracetam are known to interact with the synaptic vesicle protein 2A (SV2A) (Lynch et al., 2004) and may regulate or increase its expression. Since SV2A knockout animals or mice with missense mutations of SV2A have severe seizures, these drugs may regulate the expression of the Ca^{2+} sensor protein Syt1 and may change the sensitivity of synaptic vesicles to Ca^{2+}, specifically affecting the modulation of GABA release in the hippocampus (Tokudome et al., 2016). In humans, these drugs have shown promising results as Levetiracetam administered to patients suffering from mild cognitive impairment (which often progress to AD), results in reduced hippocampal hyperactivation measured by BOLD levels, and improves performance in a memory task (Bakker et al., 2012).

Medications that restore E/I balance which are already clinically approved could be potentially repurposed as valuable disease-modifying treatments for AD and should be taken into consideration. One such example is Acamprosate, a synthetic GABA analog that is thought to interact with NMDARs (Qatari et al., 1998). Acamprosate is often prescribed as an anti-craving medication to prevent alcohol relapse, can decrease glutamate levels and reduce hyperexcitability (Dahchour et al., 1998; Kalk and Lingford-Hughes, 2014; Umhau et al., 2010). Other examples include Baclofen, a $GABA_B$ receptor agonist, which in conjunction with Acamprosate is currently being tested in AD patients (Chumakov et al., 2015).

Beyond pharmacology, novel therapies such as deep brain stimulation (DBS), a neurosurgical procedure able to focally modulate circuit activity, are being developed (Lozano et al., 2016; Smith et al., 2012), but a systematic characterization of how these stimulation methods affect E/I balance and memory mechanisms will be critical for the efficient development of optimal stimulation protocols for AD.

6. Conclusions and outlook

Although it is becoming increasingly clear that an E/I imbalance and epileptic activity may be an early stage dysfunction in the brains of AD patients, non-convulsive network anomalies may have gone unnoticed and undiagnosed in the patient population and it is not apparent when and how these anomalies start or progress. Despite an increased number of studies pointing to multiple alterations to excitatory and inhibitory mechanisms, the interrelation between these systems and how their interaction progressively changes should be considered from the context of AD. Before plaques are present in AD brains, APP and amyloid beta are able to disrupt both glutamatergic and GABAergic signalling, upsetting the networks' fine excitatory-inhibitory balance. Glutamate uptake and enhanced glutamatergic signalling via changes in NMDARs and mGluRs are involved in synaptic dysfunction in the early stages of AD and blocking these receptors pharmacologically show promising results. Recent research has also highlighted the changes in GABAergic innervation and impaired firing of fast-spiking GABAergic neurons, and how antiepileptic drugs may be able to abolish hyperexcitability and ameliorate cognitive decline. Finally, the importance of astrocytes in balancing the system by reversing GABAergic transport function and increasing GABA synthesis should also be considered, as astrocytic alterations are detected early on in patients. These results suggest that determining the effect and causes leading to neuronal network imbalance in neurodegenerative diseases is an important question that spans beyond neuronal death and can lead to the development of potential therapeutic targets.

Based on results from recent anti-amyloid clinical trials, it has become apparent that reducing Ab levels in the later stages of AD is unlikely to result in better patient outcome, highlighting the need to develop useful preclinical biomarkers. The use of additional treatment approaches to modulate early E/I imbalance in AD may offer promising disease modifying strategies. Further studies on the effect of antiepileptic drugs and other inhibitory modulating drugs in AD should be considered.

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