Ghulam Abbas*, Wajahat Mahmood and Nurul Kabir

Recent progress on the role of GABAergic neurotransmission in the pathogenesis of Alzheimer’s disease

DOI 10.1515/revneuro-2015-0062
Received November 7, 2015; accepted November 29, 2015

Abstract: Despite their possible causative role, targeting amyloidosis, tau phosphorylation, acetylcholine esterase, glutamate, oxidative stress and mitochondrial metabolism have not yet led to the development of drugs to cure Alzheimer’s disease (AD). Recent preclinical and clinical reports exhibit a surge in interest in the role of GABAergic neurotransmission in the pathogenesis of AD. The interaction among GABAergic signaling, amyloid-β and acetylcholine is shown to affect the homeostasis between excitation (glutamate) and inhibition (GABA) in the brain. As a consequence, over-excitation leads to neurodegeneration (excitotoxicity) and impairment in the higher level functions. Previously, the glutamate arm of this balance received the most attention. Recent literature suggests that over-excitation is primarily mediated by dysfunctional GABA signaling and can possibly be restored by rectifying anomalous metabolism observed in the GABAergic neurons during AD. Additionally, neurogenesis and synaptogenesis have also been linked with GABAergic signaling. This association may provide a basis for the needed repair mechanism. Furthermore, several preclinical interventional studies revealed that targeting various GABA receptor subtypes holds potential in overcoming the memory deficits associated with AD. In conclusion, the recent scientific literature suggests that GABAergic signaling presents itself as a promising target for anti-AD drug development.

Keywords: acetylcholine; amyloidosis; GABA; metabolism; neurogenesis; synaptogenesis.

Introduction

Alzheimer’s disease (AD), named after German neuropathologist Alois Alzheimer (1906), is a neurodegenerative disorder that affects memory, cognition and behavior. Global estimation revealed that it will victimize 1 in 85 by 2050 (Brookmeyer et al., 2007). It progresses insidiously and cuts short the average life expectancy to about 7 years following diagnosis (Mölsä et al., 2009). Various hypotheses have been proposed for explaining the underlying pathology of AD, such as amyloidosis, Tau phosphorylation, oxidative stress, dysfunctional cholinergic/glutamatergic signaling and mitochondrial (energy) alterations (Castellani and Perry, 2012). However, decades of research involving the aforementioned associations have not really led to the development of drug(s) that can cure this ailment. The possible reason for this failure could be the oversimplification of the etiology of AD. For example, among the aforementioned associations, amyloidosis has received the most attention but amyloid-induced neurodegeneration is reported to be mediated via neurofibrillary tangles (Iwatsubo, 2006). Some researchers are in favor of neurofibrillary tangles to be the major determinant of AD (Giannakopoulos et al., 2003). Moreover, β-amyloid (Graham et al., 1996) and neurofibrillary pathology (Feany and Dickson, 1996) are not specific to AD. Recently, it was reported that neuritic plaques mainly constitute of N-terminally truncated Aβ-peptides that originate from the glial cells (astrocytes and microglia). Notably, this isoform of Aβ-peptide is not affected by β-secretase inhibition (Oberstein et al., 2015). One of the more interesting reports suggested that Aβ-peptide is a physiological (not pathological) player in the synapse, and its alteration observed during AD is nothing more than a compensatory response generated by the body to maintain its executive functions (Koudinov and Berezov, 2004). During literature search, we note with caution that most of the β-amyloid (Graham et al., 1996) and neurofibrillary pathology (Feany and Dickson, 1996) related works were performed on primary neuronal cultures where the complex interactions mentioned above are most likely absent. The aforementioned
perplexing Aβ-peptide related studies and the failure of the relevant clinical trials critically illustrate the need for continue investigating newer mechanisms underlying the pathogenesis of AD. Partly because of this reason, the present review is presented to the readers for a better understanding of the complex interactions among cholinergic, glutamatergic and GABAergic systems that may underlie the pathogenesis of AD (Nelson et al., 2009).

GABA is the major inhibitory neurotransmitter in the brain. Two main classes of receptors have been identified i.e. GABA<sub>A</sub> and GABA<sub>B</sub>. The former is ionotropic, the activation of which leads to the opening of a transmembrane chloride channel leading to hyperpolarization. The latter is a presynaptic regulatory receptor and belongs to the metabotropic class of inhibitory Gi-protein-coupled receptors (Watanabe et al., 2002). Despite the earlier belief that the inhibitory pathways in the brain remain unaffected in AD, several reports have revealed the possible role of GABAeric signaling in the pathogenesis of AD. For example, the functional loss of GABA<sub>A</sub> receptors was reported in the brains of AD subjects (Limon et al., 2012). Recent literature revealed the upsurge in reports exhibiting the role of GABAergic neurotransmission in the pathogenesis of AD.

**Amyloid-β, acetylcholine (ACh) and GABA**

The amyloidosis hypothesis states that the synaptic dysfunction and impaired cognition observed in AD are mediated via accumulation of Aβ-peptides, generated from the cleavage of amyloid-β protein precursor (AβPP, a ubiquitous type I membrane glycoprotein) (Nalivaeva and Turner, 2013). In the nerve terminals of the rat hippocampus, AβPP abundance was shown to be in the order of glutamate>GABA>ACh (Rodrigues et al., 2014). We note that the modulators of glutamatergic and cholinergic signaling are already in market. The former (NMDA antagonist e.g. memantine) slows down the progression of AD, while the later (ACh esterase inhibitors e.g. donepezil, galantamine, rivastigmine and tacrine) provides symptomatic relief. However, none of them offer a real cure and are ineffective in the long run. The neurotoxicity of soluble Aβ aggregates has been primarily attributed to excitatory neurotransmission systems. Nevertheless, the presence of AβPP in GABAergic nerve terminals highlights the importance of yet unexplored inhibitory pathways in AD. In this regard, neuroprotection against Aβ toxic effects has been described by NMDA receptor blockade with MK801 supporting the idea that a persistent hyperpolarization can reduce the Aβ neurotoxicity due to inactivation of NMDA receptors (Rodrigues et al., 2014). The affinity of amyloid-β towards inhibitory input was further strengthened by reports exhibiting suppression of long-term potentiation (the popular Hebbian’s basis of learning and memory) (Jo et al., 2011) but not long-term depression (Wang et al., 2002). Among the various subtypes of the nicotinic receptors, α4/7 and β2 are instrumental in spatial memory related tasks (Levin, 2002). In the CA1 hippocampal region, the aforementioned Aβ mediated suppression of LTP was reported to be dependent on the α4/β2 nicotinic ACh receptors (Wu et al., 2008). Several reports exhibited the interaction between GABAergic and cholinergic signaling. The GABAergic neurons of the medial septum-diagonal band of Broca (MSDB) play an important role in forming spatial working memory. Lesions in this region were shown to affect the release of ACh from the hippocampus during memory related tasks. Thus, GABA modulates hippocampal ACh efflux under condition of memorizing load (Roland et al., 2014). Furthermore, the stimulation of the α7 nAChR was shown to enhance the GABAergic synaptic activity in hippocampal slices (Hajos et al., 2005). The amyloid-β administration was shown to decrease the number of α7 nicotinic ACh receptors in the GABAergic neurons of the MSDB (Gonzalo-Ruiz and Arévalo-Serrano, 2014). The density of this receptor subtype was also reported to be decreased in the brains of AD patients (Lee et al., 2000). Its aforementioned down regulation may decrease the inhibitory input and shift the balance towards excitatory neurotransmission leading to neurodegeneration. The α7 nAChR nicotinic receptor has been considered as the target for curing cognitive disorders (Mansvelder et al., 2006) because it enhances the vulnerability of pyramidal cholinergic neurons by increasing the accumulation/internalization of Aβ (D’Andrea and Nagele, 2006). Having said that, the readers are suggested to see reviews discussing the perturbation of excitatory-inhibitory imbalance as underlying cause of neurodegenerative ailments such as AD (Rissman and Mobley, 2011; Nava-Mesa et al., 2014) and amyotrophic lateral sclerosis (Schütz, 2005). This imbalance was also reviewed to affect adult brain plasticity (Baroncelli et al., 2011), neurogenesis (Saaltink and Vreugdenhil, 2014) and aging/cognitive decline (Majdi et al., 2009). The disruption of this balance has also been attributed to GABA<sub>A</sub> receptor trafficking/mutations (Smith and Kittler, 2010). The role of the aforementioned imbalance in AD was also supported by a report that showed that the endogenous zinc...
suppressed T-type Ca\(^{2+}\) channel-dependent GABAergic signaling in the dentate gyrus, thereby creating inequality in GABA/glutamate inputs leading to neurodegeneration (Grauert et al., 2014). In similar lines, zinc is reviewed to play a critical role in neurodegeneration (Cuajungco and Lees, 1997). In contrast to the aforementioned descriptions, amyloid-\(\beta\) administration was also shown to cause the endocytosis of NMDA receptors (Snyder et al., 2005). This can be explained as a homeostatic response to the over-excitation caused by A\(\beta\). The interaction between GABAergic and cholinergic neurons was further supported by the fact that inactivation of GABAergic neurotransmission can also lead to cholinergic dysfunction in the basal forebrain (BF, involved in activation and attention) (Yang et al., 2014). This dysfunction can affect executive functions such as cognition, learning and memory. This shows that both cholinergic and GABAergic systems functionally affect each other in different key brain areas involved in AD. This dual interaction is explained in detail in Figure 1. The aforementioned literature suggests that A\(\beta\) may directly or indirectly (via cholinergic system) affect the activity of the GABAergic neurons. The resultant over-excitation leads to excitotoxic damage in the brain. Hence, the GABAergic neurotransmission presents itself as a potential target for restoring the imbalance between excitation and inhibition in the brain of AD subjects.

**Metabolism of GABAergic neurons**

Several preclinical and clinical reports have revealed altered metabolism of the GABAergic neurons in AD. Decrease in the activity of the citric acid cycle (responsible for ATP formation) and amino acids synthesis was found in various brain regions in an animal model of AD (McGill-R-Thy1-APP rat model) (Nilsen et al., 2014). In superior frontal gyrus, hippocampus and cerebellum of postmortem brain samples, arginine metabolism was found to be dysfunctional, thereby affecting the levels of GABA (Liu et al., 2014). The decrease in the levels of GABA was also supported by a reduction in glutamate decarboxylase 65 (GAD65, responsible for conversion of glutamate to GABA) in the middle temporal gyrus, hippocampus and putamen of AD subjects (Schwab et al., 2013). The aforementioned alterations can disturb GABAergic neurotransmission, which may enhance the excitatory pathways. Hence, the restoration of the inhibitory input by correcting the metabolism in the GABAergic neurons can serve as a target for developing newer anti-AD drugs.

**Neurogenesis and synaptogenesis**

The formation of new neurons and synapses is required as a part of repair mechanisms in the brain. In this regard, the aforementioned A\(\beta\)-induced imbalance in GABA and glutamate inputs was shown to cripple adult neurogenesis in a preclinical AD model (Sun et al., 2009). Hence, the restoration of this balance can bolster the needed repair mechanism in AD. Furthermore, the interaction between GABA and apolipoprotein (apo) E may also serve the purpose. Apolipoprotein E has been shown to be involved in lipid and cholesterol transport as well as cell repair, A\(\beta\)-peptide deposition and neurogenesis. The polymorphism of its genes is considered as a major risk factor for AD. Of the isoforms that are essential for lipid homeostasis, carriers of apo E4 are at higher risk for developing AD (Koutseff et al., 2014). Interestingly, the apoE4 knockout mice-induced inhibition of hippocampal neurogenesis was shown to be mediated via the impairment of the presynaptic GABAergic signaling while potentiating GABAergic signaling normalized the neuronal maturation and neurogenesis in apoE4-KI mice (Li et al., 2009). In a similar fashion, the induction of GABA\(_{\alpha}\) receptor dysfunction (via deleting \(\gamma2\) subunit) in immature neurons hampered adult neurogenesis without affecting their proliferation (Earnheart et al., 2007). In contrast, GABA\(_{\alpha}\) receptor activation was reported to inhibit neural stem...
cells proliferation and differentiation while its antagonist promoted it (Giachino et al., 2014). As mentioned earlier, GABA\textsubscript{A} receptors are regulatory in nature and their inhibition enhances the release of GABA, which appears to be a critical signal for growth, proliferation and neurogenesis. Hence, the GABA neurotransmitter directly or indirectly could affect the phenomenon of neurogenesis and can be manipulated to offer cure in AD.

Moreover, Wnt signaling has also been shown to play an important role in the formation and maintenance of the synapses. In an animal model of AD (APP/PS1-transgenic mice), Wnt signaling activation ameliorated memory impairment and enhanced synaptic function (Vargas et al., 2014). Recently, the interaction between Wnt 5a and GABA\textsubscript{A} receptors is reported in the hippocampal neurons, which play an important role in the pathogenesis of AD. Briefly, Wnt 5a was shown to increase the surface localization and clustering of GABA\textsubscript{A} receptors through calcium/calmodulin-dependent kinase II (CaMKII) (Cuitino et al., 2010). Although the outcome of the aforementioned troika (AD, Wnt and GABA) in the hippocampus is yet to be explored, this interaction needs to be focused in the context of modulating synaptogenesis, which can play a crucial role in reversing the pathology of AD.

### Interventions

Several interventional studies revealed the association between GABAergic neurotransmission and AD (Table 1). GABA receptors, especially GABA\textsubscript{A}, are well known as a target for benzodiazepines, the anxiolytic drugs with cognition lowering potential (Reynolds et al., 2012). Presumably, GABA receptors are generally ignored as a target for cognition enhancing drugs. However, the functional insight into the GABA\textsubscript{A} receptor subtypes has changed the entire paradigm. The \(\alpha 5\) subunit is the most abundant subtype of GABA\textsubscript{A} receptor in the hippocampus (Möhler, 2007), and its stimulation was reported to enhance memory (Rudolph and Möhler, 2006). The \(\alpha 5\) GABA\textsubscript{A} receptor agonist not only improved the performance of mice in Morris water maze but also enhanced long-term potentiation. Importantly, this agonist was free from convulsive side effect of benzodiazepines (Atack et al., 2006), thereby reflecting the importance of subtype selectivity in therapeutics. Furthermore, the previously ignored metabotropic GABA\textsubscript{B} receptor also gained attention. Decades ago, its inverse agonist was shown to enhance cognitive performance in rodents and primates (Mondadori et al., 1993). This negative co-relation is recently endorsed by another report in which GABA\textsubscript{B} receptor expression in the prefrontal cortex was shown to affect the working memory performance in aged rats (Bañuelos et al., 2014). In humans, the GABA\textsubscript{B} receptor antagonist was also shown to be beneficial for cognitive impairment (Froestl et al., 2004). Literature revealed that GABA\textsubscript{B} receptor regulates the voltage gated calcium channels. Therefore, the aforesaid role of zinc in disturbing the excitatory-inhibitory balance may be mediated by the GABA\textsubscript{B} receptors (Grauer et al., 2014). It is important to note that GABA\textsubscript{B} is a pre-synaptic auto-receptor and blocks the physiological release of GABA in the synapse. Its blockade would presumably increase the inhibitory input and thus can protect neuron from over-excitation, the needed phenomenon in neurodegeneration. The aforementioned reports suggest that the dissection of the GABA modulating drugs on the basis of types and subtypes can provide lead molecules for anti-AD drug development. It is important to note that several GABA modulating drugs are already in clinical use for diseases other than AD (McCarson and Enna, 2014) and needs to be tested (drug repurposing/repositioning) in patients with AD for their efficacy. A structure activity relationship approach on these existing molecules for increasing their affinity towards GABA\textsubscript{A} subtype (\(\alpha 5\)) and GABA\textsubscript{B} is worthy of investigation.

### Table 1: Effect of the various GABAergic modulators on cognition, neuroprotection, learning and memory.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>MOA</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Normalize GABA levels</td>
<td>Ameliorate memory deficits in animal model of Down’s syndrome (T56SDn)</td>
<td>Begenisic et al., 2014</td>
</tr>
<tr>
<td>AC-3933</td>
<td>Benzodiazepine receptor antagonist</td>
<td>Ameliorate scopolamine induced amnesia</td>
<td>Hatayama et al., 2014</td>
</tr>
<tr>
<td>AC-3933</td>
<td>Increase ACh release</td>
<td>Improve cognitive function</td>
<td>Hashimoto et al., 2014</td>
</tr>
<tr>
<td>Bryostatin-1</td>
<td>Enhance GABAergic neurotransmission</td>
<td>Nootropic and neuroprotective in rat model of AD</td>
<td>Xu et al., 2014</td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>GABA\textsubscript{A} receptor potentiation</td>
<td>Neuroprotective in cortical cultures</td>
<td>VandeVrede et al., 2014</td>
</tr>
</tbody>
</table>

### Conclusion

A\(\beta\) and ACh affect GABAergic neurotransmission, leading to imbalance between excitatory (glutamate) and
inhibitory (GABA) inputs of brain. The resultant overexcitation causes neurodegeneration, which manifests itself as loss of the higher level functions, as observed in patients with AD. The aforementioned imbalance could also originate from a dysfunctional metabolism inside GABAergic neurons. The restoration of this disparity via restoring GABAergic neurotransmission can possibly cure AD patients. Furthermore, the GABA neurotransmitter directly or indirectly (via apo and Wnt) modulates the phenomenon of neurogenesis/synaptogenesis, which can be yet another target for the development of anti-AD drugs. Additionally, several GABAergic neurotransmission modulating molecules have shown potential against AD in pre-clinical studies and should be further tested in AD patients. In this regard, the emerging GABA receptor types/sub-types functional knowledge can help in choosing the right molecule for clinical trials. In conclusion, there are several mechanisms through which GABAergic neurotransmission can affect the progression of heterogenous AD and can serve as a potential target for future anti-AD drugs.

Acknowledgments: This article was partly supported by a grant to Nurul Kabir, UMRG RG315-14AFR, from the University of Malaya.

Conflicts of interest statement: The authors declare that they have no conflicts of interest.

References


