A review of the complex roles of glial cells in Alzheimer’s disease and potential glial-oriented therapeutic targets

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Abstract: The pathogenesis of Alzheimer’s disease (AD) is very complicated and not well-understood. As more and more studies are performed with regards to this disease, new insights are coming to light. Much of the research in AD so far has been very neuron-oriented however, recent studies suggest that certain glial cells i.e. microglia, astrocytes, oligodendrocytes, and NG2 glia are linked to the pathogenesis of AD and may offer several potential therapeutic targets in the long-standing battle against AD. Glial cells are responsible for maintaining homeostasis (i.e. concentration of ions and neurotransmitters) within the neuronal environment of the central nervous system (CNS) and are crucial to the integrity of neurons. This review explores the (1) role of glial cells in AD pathogenesis, (2) complex functionalities of the components involved and (3) potential therapeutic targets that it could eventuate leading to a better quality of life for AD patients.

Keywords: Glial Cells, Astrocytes, NG2 Glia, Microglia, Oligodendrocytes, Alzheimer’s disease, Neurodegenerative disease, Aβ-peptides

1. Introduction

A debilitating neurological disorder, Alzheimer’s disease is characterized by beta-amyloid (Aβ) and hyper-phosphorylated tau protein aggregation in the brain leading to a loss in cognitive ability and eventually dementia [1]. Since one of the greatest risk factors of AD is increasing age it is often manifest in many patient populations throughout the world. The approximate number of patients with AD in 2010 was 35 million and this number is projected to rise to 65 million in 2030. The prevalence of AD is almost double in human males compared to females and after the age of 85 the occurrence of AD is seen in almost 50% of the demographic [1]. AD can be classified into two different subgroups based on the age of onset of the disease. Familial AD (FAD) occurs at an early age of onset and sporadic AD (SAD) occurs at a much later age. FAD is a rare autosomal dominant genetic disorder that accounts for only a minor portion of AD cases. FAD symptoms appear in patients between the age of 30 and 50; and this specific disorder is characterized by mutations in amyloid precursor protein or presenilin 1 and 2 genes. SAD accounts for the majority of AD cases and the usual age of onset is observed to be 65 onwards. Even though the underlying mechanism of SAD still remains unknown, SAD has been linked to mutations in the Apolipoprotein E (ApoE) gene [2,3]. There are several methods of assessment available for AD patients, including tests of episodic memory and attention but a more definite diagnosis of AD can only be made post-mortem histological analysis. These analyses often reveal cerebral cortical atrophy, amyloid plaques, neurofibrillary tangles (NFTs) and vascular amyloidosis that collectively represent Aβ peptide deposits in the brain [4,5]. Much of the research on AD so far has been very neuron-oriented but in recent times, the interest in glial cells in this particular topic is markedly increasing
1. Overview of the role of glial cells in AD:

Looking at the nervous system from a broad perspective, it is built using two types of cells i.e. neurons and glial cells. Glial cells are the majority in terms of numbers even though they occupy similar amount of space in the nervous tissue. The glial cells involved in the nervous system are: oligodendrocytes, polydendrocytes (NG2 glia), astrocytes, Schwann cells, satellite cells, microglia, ependymal cells and enteric glial cells. These glial cells function to maintain homeostasis (i.e. concentration of ions and neurotransmitters) within the neuronal environment, aid in the formation of myelin sheaths around the axons in the nervous system responsible for the cell-to-cell signaling and maintain the function of synapses [6]. When this homeostasis is disrupted the progression of neurodegenerative diseases such as AD may be accelerated [6]. Researchers in neuroscience disciplines have put in considerable amount of effort and managed to limn the importance of glial cells AD research through the in vivo studies in various animal models.

1.2. In vivo models used for the study of AD:

Animal models, especially murine models have been widely used in the studies regarding AD pathogenesis. SAD is the more common form of AD that is more complicated to study compared to FAD. However, studying FAD is somewhat more feasible to observe in murine models. If there is an underlying assumption that the two of types of AD have similar genetic origin, then AD may be studied more practically using these models. Some murine models that have been pivotal in identifying the neuropathology of AD [7–16]. studies on specific types of glial cells have been done on specific mouse models. In order to piece together the information accurately the murine models and their studied alterations in glial cells and neurons are depicted in Table 1. These are just a few examples and a comprehensive guide to these murine models and relevant findings can be found in the Alzforum website (https://www.alzforum.org/research-models) where a database was created to aid in AD research.

Table 1. Some well-studied murine models for AD and observed alterations in specific types of glial cells

<table>
<thead>
<tr>
<th>Murine Model</th>
<th>Observed loss of neurons</th>
<th>Observed alteration in microglia</th>
<th>Observed alteration in astrocytes</th>
<th>Observed alteration in oligodendrocytes</th>
<th>Observed alteration in NG2 glia</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDAPP-J20</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Tg2576</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>APP23</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>APP NL-F</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>APPswePS1dE9</td>
<td>×</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>5xFAD</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>3xTg-AD</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
</tbody>
</table>
These models are indeed helpful in terms of looking at the pathogenesis of AD but more importantly these may give some insight into the potential therapeutic targets that may exist. However, it is worthwhile to notice that these models do not accurately mimic AD and the many complexities it creates. Moreover, there could be several problems related to the interpretation of these kinds of data from animal models to humans that may obfuscate the lucidity of the observed phenomena. For example, in some of these models, fragments of APP, such as intracellular cytoplasmic domain (AICD) or α-secretase cleaved secreted APP (α-APPα) may also show overexpression along with APP. These fragments may exhibit some functions in the host that may be observable clinically. For example, in Tg2576 mice (shown in Table 1), the overexpressed α-APPα upregulates insulin like growth factor-2 (IGF-2) and protein transthyretin (TTR) that may lead to some neuroprotective properties for the mice. This may be one of the reasons why these mice often do not show a significant amount of neuronal loss [17]. Another reason the interpretation may be hard is that wild-type mice that overexpress APP may show cognitive decline even without Aβ deposits being formed in the brain [18]. The interpretation become even more nebulous for a modeled organism when, due to alternative splicing, the transgene mRNA of APP might be altered and the composition may differ from endogenous APP; this becomes even less manageable when the variability across different organisms is taken into account. This variability is an issue since the models are usually selected by looking at the phenotype similarity between the model and human [19,20]. Regardless of the challenges, murine models have been a useful tool in identifying the roles of various glial cells in the pathogenesis of AD and this review will focus on these individual cell types and their potential therapeutic applications separately.

2. Microglia

Microglia is an essential part of the substructure that is responsible for maintaining the homeostasis within the neuronal environment. Microglia are ubiquitous in the central nervous system (CNS) and more senescent they become they become increasingly less able to perform their cellular functions [21]. It has been observed that the physiological decline in microglia in proportion to the age of the brain in humans is similar to the decline in function in AD. However, these changes are more pronounced in AD patients. Microglia pathogenesis is accompanied by the release of neurotrophins or inflammatory cytokines which may have detrimental or supportive effect on neurons [22–24]. In murine animal models, it has been observed that morphological changes in microglia occur at a higher degree in aged mice compared to their young counterparts. Usually microglia morphology can switch between an “active” state and a “resting” (ramified) state. In aged mice, these cells become less ramified and more “active”, cause neuronal hypertrophy and become less active in the CNS; more specifically in the corpus callosum, striatum, substantia nigra, dentate gyrus, cerebellar nuclei, inferior cerebellar pendule and the molecular layer of the cerebellar cortex [25,26]. Mouse models that overexpress mutated version of human APP show that these morphological changes in the microglia appear around six months’ time and are accompanied by a loss of activity in the brain parenchyma [27]. In PDAPP-JO mice these changes start manifesting as early as 3 months’ time [ibid]. In the healthy aged brain, microglia are the main source of pro-inflammatory cytokines such as TNFα, IL1β, IL1α, IL6, nitric oxide etc. [28–31]. During AD pathogenesis, they also release IL-4, IL-10, IL-13 and transforming growth factor (TGF)-β1. Studies done on murine models indicate that the increased production of these cytokines may damage neurons in their vicinity especially since a decrease in TGF-β1 was observed in models that
underwent Aβ clearance by phagocytosis during AD pathology [31]. Since the release of these cytokines and phagocytosis are the main functions of activated microglia, researchers have also looked into Ca\(^{2+}\) signaling that is responsible for their regulation. A recent study in APPPS1 mice as well as in AD patients revealed that the intracellular concentrations of Ca\(^{2+}\) are noticeably increased in the activated microglia around Aβ plaques tending towards the conclusion that the increase in Ca\(^{2+}\) signaling is associated with neurodegeneration in AD patients [32–34].

Even though the role of microglia seems to be very relevant to the conversation, the problem of interpreting the results of these models accurately to humans still remains a challenge however. Studies done on human Alzheimer’s disease tissue (hAD) suggest that Aβ deposits do not directly trigger microglial activation, rather their progressive degeneration and subsequent loss of neuroprotection may contribute towards to the onset of AD cases [24,35]. These findings contradict the mouse model inferences that microglial activation and neuro-inflammation contributes towards AD phenotype. Another issue that researchers are having to constantly go back and forth on is in the case of microglia proliferation. Some studies show that the cellular proliferation may contribute towards AD pathogenesis while others argue against it. For example, it was recently identified when hippocampus of 3xTg-AD mice were compared with human hippocampus of control subjects in which the microglial proliferation observed in the mice were not seen in the human subjects [36]. In contrast, another study revealed that there was an increased number of microglia present in the temporal cortex of human AD patients compared to their non-demented control groups [37]. To date the best consensus seems to be that that the phenotypic changes in the microglia are of more importance compared to the increased proliferation rates in AD patients.

Evidence indicate that the morphological changes of microglia may be reversed by Aβ vaccination which may reduce Aβ deposits overall [27]. In addition to morphology, genetic studies have revealed that variations in genes that responsible for encoding microglial proteins are strongly related to AD pathogenesis. In a recent study with APPSwe/PS1dE9 mice, it was observed that the gene TREM2 (Triggering Receptor Expressed on Myeloid Cells) is upregulated in microglia and becomes more pronounced as AD progresses [38]. Even though originally TREM2 was identified as a risk gene for AD, this study showed that TREM2 may indeed facilitate Aβ phagocytosis and in turn improve patient cognitive functions by slowing down AD progression by increasing neuroprotection. Therefore TREM2 may eventually become a potential therapeutic target in terms of glial cell oriented therapy for AD.

3. Astrocytes

In the human brain, the circuitry is formed by neuronal networks which are embedded in astroglial syncytia. Astrocytes have numerous functions which include assisting in neurogenesis, maintaining overall homeostatic in the brain, structuring the grey matter etc. In the early stages of neurodegenerative diseases or brain injuries, astrocytes often atrophy and in the later stages, they become activated and may cause neuroinflammation that contribute towards neurodegeneration and cell death [39]. Studies on hAD tissues and APPswePS1dE9 mice have confirmed that astrocytes in the brain of AD patients upregulate immune response through gene activation and contribute towards chronic inflammation and associated oxidative stress that may cause irrevocable cell damage and ultimate cell death [40,41]. Astrocytes most abundant non-neuronal cells in the CNS and they modulate activity of synapses and moderate local blood flow through Ca\(^{2+}\)-dependent cell signaling [42]. During progression of AD, astrocytes go through noticeable morphological changes. These phenomena are observed in studies of brain tissue of 3xTg-AD mice where astrocytes in the entorhinal cortex show marked atrophy at the early stages i.e. around 1 month well ahead of detectable Aβ plaque formation [43]. In the same mice, after considerable AD progression and the development of extracellular plaques, the atrophy is still observable even when the astrocytes are not in contact with the plaques [44]. However, in terms of number, there is no marked differences in the rate of proliferation or degeneration when AD human brain tissue was compared to healthy
control group tissue via post-mortem analysis [45–47]. The formation of Aβ plaques in AD patients often results from a lack of Aβ clearance [48]. Astrocytes are responsible for enlisting several enzymes such as neprilysin (NEP), angiotensin-converting enzyme (ACE), endothelin converting enzyme (ECE), insulin degrading enzyme (IDE) and matrix metalloproteinases that degrade Aβ plaques [49–51].

Researchers have posited a possible explanation of the roles of astrocytes in the early stages of AD by inferring that when astrocytes detect Aβ released by affected neurons, they withdraw their support from the all the neurons in the vicinity creating a feed forward loop that results in the acceleration of Aβ plaque formation [52]. Studies done on hAD samples show similarly that during AD progression, astrocytes are responsible for accumulating Aβ and when overloaded, form their own Aβ plaques when they undergo lysis [47]. Astrocytes may upregulate the protein known as glial fibrillary acidic protein (GFAP), which modulates immune response in the CNS, usually to neurodegeneration or traumatic brain injury [53,54] Studies in APP/PS1 mice have shown that the deletion of GFAP which inhibits astrogliosis showed a marked increase in Aβ plaque formation thereby confirming the role of astrocytes in Aβ degradation [55]. However, astrogliosis may not always be beneficial in the sense that sustained proliferation of astrocytes during AD progression has been correlated with an increase of NFTs in human brain tissue [56].

3.1. Astrocytic Ca²⁺ homeostasis in AD:

A significant amount of evidence suggests that Ca²⁺ homeostasis is often altered by Aβ. Murine model studies have revealed that astrocytes in Aβ overloaded tissue have increased concentration of Ca²⁺ [57]. In mouse models, these abnormal Ca²⁺ concentrations have been shown to be associated with the increased activation of P2Y1 receptors and transient receptor potential channel 4 [58,59]. In 3xTg-AD mice, Ca²⁺ release is observed from the endoplasmic reticulum (ER) of astrocytes by Aβ following stress on the ER [60]. Increased concentration of Ca²⁺ activates phosphatase calcineurin (CaN) and downstream targets for example, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and nuclear factor of activated B cells (NFAT). In Tg2576 mice, NFAT or CaN inhibition decreases neuronal degeneration induced by Aβ [ibid]. Also evidence from studies in rat primary astrocytes suggest that CaN activation may contribute towards Ca²⁺ overload [61,62].

3.2. Astrocytic function and neurotransmitters in AD:

At the synapse, the clearance of excess glutamate, its conversion to glutamine and the re-synthesis of glutamate is one of the primary astrocytic functions. Glutamate aspartate transporter (GLAST), glutamate transporter – 1 (GLT-1) and glutamine synthase (GS) is expressed by these cells for the purpose of maintaining this glutamate homeostasis. In 3xTg-AD mice and hAD samples, GS expression is attenuated by the progressive formation of Aβ [63,64]. In the hippocampus and cortex of AD patients, there is a noticeable decrease in GLT-1 expression which is further evidence of this disruption in glutamate homeostasis [65]. This disruption may be play a role in glutamatergic transmission and neuronal damage in AD. Moreover, studies on the cerebellum of healthy murine models show that astrocytes release GABA through bestrophin channel (Best 1) which inhibit synaptic function; GABA (γ-aminobutyric acid) is a primary neurotransmitter in the mammalian CNS [65]. From the hippocampus of APP/PS1 mice, it has been observed that there is an enhancement of this Best 1-mediated release of GABA, in the vicinity of Aβ plaques, from active astrocytes indicating that Aβ plaques may play a role in increased astrocytic GABA synthesis [ibid]. Furthermore, studies on hAD samples show that there is an increased expression of monoamineoxidase B, which is a GABA-synthesizing enzyme in astrocytes, and the total number of GABA positive astrocytes as a whole further clarifying the role of GABA positive astrocytes in AD [66]. All of these findings taken together show strong correlation of astrocytes in the involvement of AD progression.
Studies done on APP/PS1 mice have shown that the inhibition of CaN/NFAT pathway in astrocytes slows down astrogliosis and consequently improves cognitive functions [67]. In 2012, Furman et al. showed that using adeno-associated virus (AAV) vectors that contained astrocyte-specific Gf22 promoter they were able to target the hippocampal astrocytes in APP/PS1 mice. The vectors stimulated the expression of VIVIT, which is a peptide that interferes with the calcineurin/NFAT pathway leading to reduced astrocytic activation. When this treatment was ran for several months, the mice showed diminished glial activation, lower Aβ levels and improvements in synaptic and cognitive function. These results are promising and warrant further exploration of novel astrocyte-based therapies for AD.

4. Oligodendrocytes

Another important class of glial cells that have been part of AD research for a significant period of time are oligodendrocytes. These cells are responsible for providing insulation and support to the neuronal axons in the CNS required for the fast action potential propagation. Evidence suggests that structural and spatial organization of myelin lipid bilayers have a strong connection with the pathogenesis of AD [68,69]. As with microglia and astrocytes, oligodendrocytes have also shown to exhibit specific morphological changes during AD progression. In PDAPP mice of age 15 months as well as hAD samples, researchers have used imaging studies and X-ray diffraction to show that near the Aβ plaques, there is noticeable deterioration in myelin integrity and axonal destruction [68,70–73]. Electron microscopy and myelin staining revealed that 3xTg-AD mice of age 2-6 months compared to control groups exhibit myelin sheath alterations and impairment of axonal morphology possibly due to a loss of oligodendrocytes [74,75]. In terms of numbers however, most studies on mouse models and hAD samples have revealed that while the myelin integrity is compromised in most cases, the overall amount of myelin largely remains unchanged [74,76,77]. When the impact of Aβ is studied on oligodendrocytes, it has been demonstrated through TUNEL staining and MTT cytotoxicity assay that the treatment with Aβ usually results in the breakdown of cell processes, shrunken cell bodies and DNA damage in these cells [78]. Aβ treatment in oligodendrocytes has also been seen to induce release of cytosolic cytochrome C and increased binding activity of AP-1 and NF-κ suggesting that oxidative stress may be, in part, responsible for cell death [78]. This cytotoxic effect of Aβ on oligodendrocytes was prevented with the introduction of LPS and INF-γ, which are pro-inflammatory in nature and also when the cells were co-cultured with astrocytes [79]. However, morphological analysis still showed persistent damage to the oligodendrocytes.

More recently, Aβ treatment on oligodendrocytes have been showed to increase in the levels of caspase-3. The accumulation of caspase-3 leads hindrance of the branching and elongation process of oligodendrocytes by blocking of the local re-organization of microtubules [80]. Park et al. demonstrated that in PS1mutK1 mice, cultured oligodendrocytes exhibit higher levels of Ca2+ concentrations compared to control groups which may be a critical factor in ultimate cell death [81]. Another recent study reported that AD progression causes an increase in the DNA damage by upregulating the growth arrest DNA damage protein (GADD) [82]. Taken together, the changes in functionality and morphology of oligodendrocytes resulting from compromised myelin integrity indicate that oligodendrocytes are also victims during AD progression and eventually contribute towards cognitive dysfunction such as impaired learning ability. However the extent of involvement of these cells largely remains unknown.

4.1. Antioxidants that may be used to treat AD:

Oxidative stress i.e. lipid peroxidation and protein oxidation, plays an important role in AD with oligodendrocytes and neurons being more susceptible compared to microglia or astrocytes. Neurons are dependent on astrocytes for the supply of glutathione (GSH) precursors; the Aβ-mediated Ca2+ disruption in astrocytes has been shown to result in the death of these neurons. Oligodendrocytes also maintain low concentrations of GSH which in conjunction with higher iron
concentrations may attenuate the ability of these cells to scavenge for reactive oxygen species (ROS).

Therefore, a reasonable link is formed between Aβ-mediated and antioxidant capacity of the CNS. N-acetylcycteine has been shown to prevent Aβ-induced cellular death in oligodendrocytes [78] whereas troxol, which is a vitamin E analog, has been shown to reduces cell death in astrocytes and neurons [58]. In addition, curcumin has been shown to increase concentrations of GSH by increasing the activity of glutamate-cystein ligase (a GSH synthesizing enzyme) potentially offering up higher neuroprotection from AD [83].

5. NG2-glia

Polydendrocytes or oligodendrocyte precursor cells (OPCs) or NG2-glia are the latest discovery in glial cell types but their role in the pathogenesis in AD are already of major interest [84]. When glial progenitor cells (GPCs), largely composed of NG2-glia, were studied in 12 and 24 month old APP23 mice, neuroblast percentage in the GPC progeny were markedly reduced compared to control mice [85]. An explanation posited for this phenomena in GPCs was that there were reduced levels of Mash1, Ngn2 and NeuroD1. In hAD sample, similar observations were seen compared to human control subjects. In addition, the GPC progeny of both models showed reduced levels of β-catenin while glycogen synthase kinase (GSK-3β), an enzyme that phosphorylates β-catenin and phosphorylated β-catenin levels were increased. In APP23 mice, the expression levels of GSK-3β was reduced accompanied by an increase in β-catenin and Ngn2 when treated with GSK-3β-siRNA. In combination with previous studies, this was evidence of the fact that Aβ activates GSK-3β resulting in the increased phosphorylation of β-catenin resulting in β-catenin degradation and the inhibition of the Wnt signaling pathway [86]. This inactivation of the Wnt signaling pathway through Aβ toxicity leads to the inhibition of the differentiation of NG2-glia [87]. However, a recent studies also suggest that Aβ does not have a direct impact on the survival rate of oligodendrocytes after the induction of NG2-glia in vitro [80]. A comprehensive investigation by Nielsen et al. of NG2-glia and human AD patients recently revealed that individuals with an overexpression of Aβ showed reduced NG2 immunoreactivity, dense cellular bodies and reduced levels in cell lysates even though cell viability remained largely unchanged. Furthermore, the group reported reduced levels of NG2 in cerebrospinal fluid (CSF) of AD patient even though there was no link with cognitive decline in those cases [88]. In contrast, another group reported that the number of NG2-glia increased in 12-15 month old APPswe/PS1dE9 mice compared to age-matched control groups. Indeed due to the lack of knowledge on the issue, the debate on the exact involvement of NG2 glia remains largely uncertain but this avenue of research may be worthy of pursuit as more and more studies are performed.

5.1. Stimulation of Wnt pathway in the treatment of AD:

Since Aβ action increases the expression levels of GSK-3β and phosphorylated β-catenin, stimulation of the Wnt/β-catenin pathway may be a potential way to mitigate AD pathology [87]. In vitro and in vivo studies, particularly on those on 3xTg-AD mice, have shown that GSK-3β inhibitor TWS119 has mitigated impaired myelination of neurons [89]. Similar stimulation of this signaling pathway may have a role in reducing glutamate excitotoxicity in astrocytes as well. In APP/PS1dE9 mice, it was seen that stimulation by pyrrolidine dithiocarbamate (PDTC) increased GLT-1 levels as well as reduced the extent of tau protein phosphorylation which is another major unidentified component along with Aβ buildup [90]. Furthermore, a recent study on APPswe/PS1dE9 mice showed that rosiglitazone or lithium caused similar stimulation and reduced astrogliosis, levels of activated microglia and Aβ plaque load [91]. Stimulation of this pathway does come at a cost however since studies on hAD samples showed that the increased levels of β-catenin and consequently the increased level of activated microglia leads to an increase in AD neuroinflammation which counteracts the enhanced Aβ clearance through phagocytosis by the same microglia [92].
6. Other potential therapeutic targets of interest

There are other approaches that are being investigated as well with regards to glial-oriented AD therapy. For example, neural stem cells (NSCs) engraftment holds much promise in AD since NSCs are responsible for producing various beneficial factors such as neurotrophic factors that promote the regeneration of the CNS as well as migrating to sites of injury and differentiating into neural cells. Studies on 3xTg-AD mice show that the engraftment increased the number of oligodendrocytes and astrocytes as well as increased levels of brain derived neurotrophic factor (BDNF) but did not alter Aβ deposition or tau protein phosphorylation [93]. Another interesting line of research has been perused through the production of Cortical GABAergic interneurons from embryonic medial ganglionic eminence (MGE) cells [94,95]. Immature progenitor cortical interneurons are produced, transported and distributed all through the hippocampus and cortex in the brain. Studies have shown that this particular structure can in fact be dissected from rodent embryos and transplanted to adult animals. The transplant recipients showed promise in several neurodegenerative disorders and these cells may become an attractive target for AD in the near future [98-109]. Furthermore, another group of researchers showed that in 5xFAD mice, the increased expression of BDNF can be induced by sodium phenylbutyrate and can repair synapses improving cognitive function [108]. In 3xTg-AD mice, intentional glial cell derived neurotrophic factor (GDNF) overexpression also showed conservation of memory and learning capability in vivo as well as decreased oxidative stress and cellular death in vitro [109]. A schematic diagram of the glial-oriented potential therapeutic agents are outlined in Table 2.

Table 2. A summary of the agents that may have therapeutic applications in AD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td>Trolox</td>
<td>Reduced death of neurons and astrocytes [58]</td>
</tr>
<tr>
<td>N-acetylcystein</td>
<td>Reduced death of oligodendrocytes [78]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Increased concentrations of GSH in neurons and astrocytes [83]</td>
</tr>
<tr>
<td>TWS119</td>
<td>Improved myelination [89]</td>
</tr>
<tr>
<td>Pyrrolidine dithiocarbamate (PDTC)</td>
<td>Increased levels of GLT-1 [90]</td>
</tr>
<tr>
<td>Lithium/rosiglitazone</td>
<td>Reduced AB load [91]</td>
</tr>
<tr>
<td>NSCs (transplantation)</td>
<td>Improved cognitive functions [93]</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>Improved cognitive functions [108]</td>
</tr>
</tbody>
</table>

7. Conclusions

The attempt to understand AD all of its complexities yielded mixed results so far but as more data becomes available, more complex and exhaustive approaches can be identified that will eventuate a more concrete understanding in the near-future. At its core, the understanding of the etiology of AD still remains an issue. It is very difficult to pinpoint the exact origin of AD and the key players involved. As of yet, no concrete therapy exists that can reverse AD progression and
researchers may have to adapt complex approaches in order to treat AD. Many treatment options have been investigated but in this review we only outlined the glial-oriented strategies that showed promise. In order to get a better understanding, a more global view of AD needs to be assimilated. A plethora of data exists for AD in terms of neuron oriented research; together with glial-oriented approaches, small pieces of information are coming out of hiding one-by-one. All of this can be taken together to piece together a more macroscopic view of AD that may answer some long standing questions that still persist. There is still long ways to go in this line of research but the glial-oriented research into AD may open new doors that can help a significant amount of AD patients around the world.

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