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Review Article

Lipid Rafts: Linking Alzheimer's Amyloid-β Production, Aggregation, and Toxicity at Neuronal Membranes

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Lipid rafts are membrane microdomains, enriched in cholesterol and sphingolipids, into which specific subsets of proteins and lipids partition, creating cell-signalling platforms that are vital for neuronal functions. Lipid rafts play at least three crucial roles in Alzheimer's Disease (AD), namely, in promoting the generation of the amyloid-β (Aβ) peptide, facilitating its aggregation upon neuronal membranes to form toxic oligomers and hosting specific neuronal receptors through which the AD-related neurotoxicity and memory impairments of the Aβ oligomers are transduced. Recent evidence suggests that Aβ oligomers may exert their deleterious effects through binding to, and causing the aberrant clustering of, lipid raft proteins including the cellular prion protein and glutamate receptors. The formation of these pathogenic lipid raft-based platforms may be critical for the toxic signalling mechanisms that underlie synaptic dysfunction and neuropathology in AD.

1. Introduction

Alzheimer's Disease (AD) is a progressive, neurodegenerative brain disorder which affects over 37 million people worldwide with an estimated global cost of over $600 billion in 2010 [1, 2]. AD is a growing socioeconomic and financial burden due to its strong correlation with ageing; around 1 in 3 people aged over 80 years have AD, which means that a rapid rise in AD cases is anticipated as life expectancy continues to increase. Although several therapeutics are currently available to slow disease progression, there is currently no way to halt or prevent AD [3].

AD is characterized by the presence of extracellular senile plaques and intracellular neurofibrillary tangles in the brain. The major constituents of senile plaques are the amyloid-β (Aβ) peptides, which are derived from the proteolytic processing of the amyloid precursor protein (APP) within lipid rafts [4]. The Aβ peptide, notably Aβ_{1-42}, is highly aggregation prone and self-assembles to form a heterogeneous mixture of oligomers and protofibrils, ultimately depositing as fibrils in senile plaques. An accumulating body of evidence indicates that soluble Aβ oligomers, which correlate strongly with disease onset and severity, are the major neurotoxic species in AD [5–8]. Although Aβ oligomers are neurotoxic at nanomolar concentrations and cause AD-related memory deficits, the cellular mechanisms of toxicity are poorly characterised. Recently, several neuronal receptors which bind Aβ oligomers have been identified, including the cellular prion protein (PrP^C) [9] and glutamate receptors [10, 11] among others. Interestingly, these receptors reside primarily within, or partition into, cholesterol-rich microdomains within the plasma membrane known as lipid rafts.

The three steps which underlie Aβ oligomer-mediated neuropathology in AD, are (1) Aβ production, (2) Aβ assembly into oligomers and (3) Aβ oligomers interacting with neuronal receptors. These steps therefore represent potential sites of therapeutic intervention in AD. Crucially, all three of these processes occur in lipid raft domains of the plasma membrane which are considered to play a key role in the development of AD [12]. In this paper, we will

outline the pivotal role that lipid rafts play in linking together the generation, self-assembly and toxicity of Aβ oligomers, which underlie the development of the neuropathology in AD. A major focus will be upon the interaction between Aβ oligomers and their putative cellular receptors.

2. Lipid Rafts

2.1. Lipid Rafts as Essential Neuronal Signalling Platforms. The multitude of different lipids and proteins within the plasma membrane were once thought to be distributed homogeneously across the entire lipid bilayer, as proposed by the fluid mosaic model in 1972 [13]. However, the plasma membrane is now known to be more akin to a sea of disordered phospholipids, in which float microdomains with distinct lipid compositions, known as lipid rafts. Lipid rafts are small (10–200 nm), heterogeneous and highly dynamic assemblies that are enriched in specific components, namely cholesterol and sphingolipids (Figure 1) [14, 15]. Biochemically, lipid rafts are defined by their relative insolubility in nonionic detergents at low temperature, conferring upon them the alternative name, detergent-resistant membranes (DRMs). Lipid rafts are also known as liquid-ordered domains because the highly saturated sphingolipid acyl chains enable closer lipid packing, and therefore more restricted lateral movement, than the mainly unsaturated acyl chains of the phospholipids in the surrounding nonraft regions of the membrane.

Functionally, lipid rafts serve to compartmentalise cellular processes by concentrating certain proteins and lipids within the same microenvironment. Lipid rafts are particularly enriched in glycosyl-phosphatidylinositol (GPI)-anchored and acylated proteins due to the preferential intercalation of the saturated acyl chains into the liquid-ordered environment [16]. Other proteins can also associate with lipid rafts either directly or through binding to other cofactors or ligands [17]. The dynamic clustering and pinching off of lipid rafts regulates the spatial and temporal assembly of signalling and trafficking molecules, forming short-lived but vital signalling platforms [17]. Lipid rafts are implicated in various essential cellular functions, including signal transduction, cell adhesion and protein/lipid sorting [18]. Of particular relevance here are cell signalling, sorting and axon guidance, as these processes are essential for neural development and synaptic plasticity [19, 20]. Crucially, neuronal lipid rafts are also required for the maintenance of dendritic spines and healthy synapses, which are vital for neural communication including learning and memory; processes which fail in AD [21]. The observation that lipid rafts are much more abundant in mature hippocampal neurons than in other cell types emphasises their physiological importance within the memory centre of the healthy brain, and may explain why hippocampal neurons are a primary target for Aβ oligomer toxicity and destruction in AD [22].

2.2. Aβ Production Is Lipid Raft Dependent. Lipid rafts are involved in the regulation of APP processing and the generation of the Aβ peptide which is the driving force in AD pathology [23, 24]. For comprehensive reviews detailing the involvement of membrane rafts in AD and Aβ production, see [25–27]. The Aβ peptide is produced by the lipid raft dependent amyloidogenic processing of its precursor protein, APP (Figure 1) [4]. The amyloidogenic cleavage of full-length APP is initiated by the β-site APP cleaving enzyme-1 (BACE1), a transmembrane aspartic metalloprotease. A large, soluble ectodomain (sAPPβ) is released to leave behind a membrane-anchored C-terminal fragment (C99) which retains the intact Aβ sequence. The second amyloidogenic cleavage of APP involves a γ-secretase complex which contains presenilin-1 or presenilin-2 (the catalytic component), presenilin enhancer-2 (PEN2), nicastrin and anterior pharynx defective-1 (APH1). The γ-secretase complex cleaves the remaining C99 stub to release Aβ peptides of between 39–42 residues in length, depending upon the precise cleavage site, along with the APP intracellular domain (AICD).

Although the majority of full-length APP is localised to nonraft regions of the plasma membrane, where non-amyloidogenic cleavage by the α-secretases ADAM 9, 10, and 17 [28] precludes Aβ formation, a subset of both APP and BACE1 partitions into lipid rafts along with γ-secretase components. Both BACE1 and the γ-secretase subunits undergo posttranslational S-palmitoylation which aids their targeting to lipid raft domains [25]. In the case of APP, a direct interaction with cholesterol—the major component of lipid rafts—was recently identified [29]. High cholesterol increases the partitioning of APP, along with BACE1 and γ-secretase components, into lipid rafts [30]. A large body of evidence points towards lipid rafts being the physiological site of amyloidogenic Aβ production by BACE1 and the γ-secretase complex. For example, both the copatching of APP and BACE1 by cross-linking antibodies [31] and the exclusive targeting of BACE1 to lipid rafts by the addition of a GPI-anchor [32] significantly increased APP cleavage at the β-secretase site. Furthermore, enrichments in lipid raft components, namely cholesterol and ganglioside GM1, promote the generation of Aβ [31, 33]. All four of the γ-secretase subunits are also enriched and active within lipid raft fractions derived from human brain [34, 35] and lipid raft-type membranes *in vitro* [36, 37]. In the brain, the majority of Aβ is found within detergent-resistant, glycolipid-enriched rafts, along with γ-secretase components [38].

2.3. Depleting Lipid Raft Components Modulates Aβ Production. The composition of lipid rafts purified from AD brains has been shown to be abnormal, with the rafts being more ordered and more viscous [39], which implies that the modulation of lipid raft composition may present a therapeutic avenue for modulating AD-related neuropathology. This has led to a number of researchers investigating whether depleting lipid raft components could lower Aβ production and therefore prevent AD. Cholesterol, being a major component of lipid rafts and a risk factor for AD, was the obvious choice to target [40]. For a recent review of the involvement of cholesterol in AD, see [41].

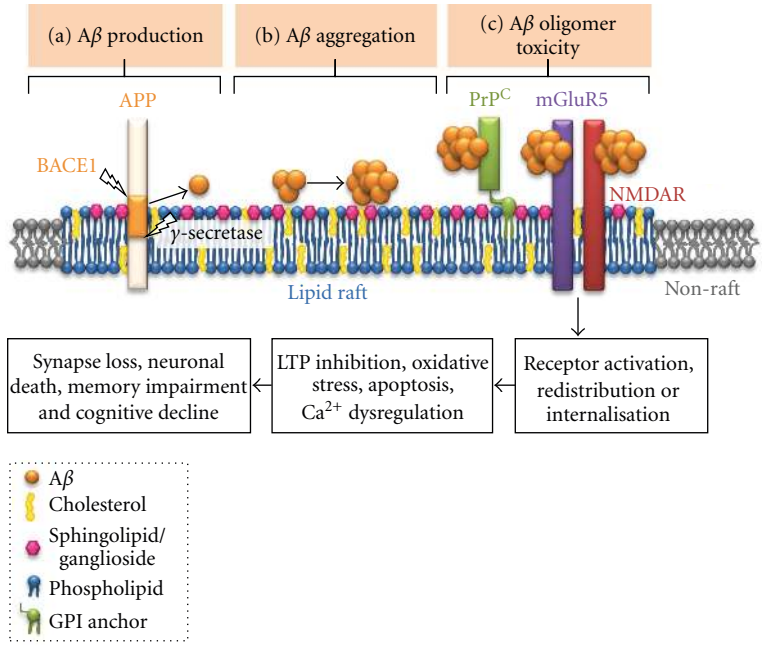


Figure 1: Lipid rafts facilitate the production, aggregation, neuronal binding and toxicity of Aβ oligomers. (a) The Aβ peptide is produced by the lipid raft dependent sequential cleavage of APP, first by BACE1 and then by the γ-secretase complex; (b) Lipid raft components including cholesterol and sialic acid-containing gangliosides promote the aggregation of Aβ to form soluble oligomers; (c) Aβ oligomers bind to specific neuronal receptors within pathogenic lipid rafts, including PrP^C and the NMDA and mGluR5 receptors. The resulting perturbations in neuronal function and survival underlie the memory impairments and cognitive decline which characterise Alzheimer's disease.

Cholesterol depletion has indeed been shown to reduce APP partitioning into lipid rafts which precludes its interaction with BACE1 and γ-secretase components, thus lowering Aβ production [42]. Hypercholesterolaemia is linked to increased Aβ production and deposition in the brain, both in humans [43–45] and in rodents [46–48] and is linked to an increased risk of developing AD. Cholesterol depletion also lowers Aβ production in cultured cells [31] and one study showed that a 70% reduction in cholesterol in living hippocampal neurons was sufficient to completely abolish Aβ production [49].

Taking this into account, cholesterol-lowering drugs known as statins have been evaluated as potential anti-AD drugs, with conflicting results [50]. Some retrospective epidemiological studies have shown that the administration of statins, which lower cholesterol levels, can reduce the incidence of dementia, including AD [51–53]. Cholesterol inhibitors can also lower Aβ levels in cultured neuroblastoma cells [54]. However, other studies have shown no correlation between statin usage and dementia [55] and the effect of statins upon disease progression and cognitive decline in AD patients has been challenged [56]. Intriguingly, it was revealed recently that Aβ production actually reduces cholesterol in cultured cells of neuronal origin by increasing efflux, possibly acting as a chaperone to remove excess cholesterol from the brain to the circulation [57].

Although a reduction in cholesterol may go some way towards reducing Aβ levels in the brain, much longer-term epidemiological studies and clinical trials initiated before significant neuronal loss and cognitive function are apparent are required in order to further elucidate the effects of lowering cholesterol levels upon AD onset and neuropathology. Lipid rafts contain many essential components other than cholesterol, such as sphingolipids, and it is likely that the modulation of just one factor will not completely abolish Aβ production *in vivo*. It is important to remember that cholesterol metabolism in the brain is largely isolated from the rest of the body by the blood-brain barrier. As nearly all of the cholesterol in the brain is synthesised *in situ*, the modulation of cholesterol levels within neurons represents a more difficult pharmaceutical challenge and the blood-brain barrier permeability of the drugs used needs to be considered [29]. Furthermore, even if cholestxerol depletion mediates a reduction in Aβ levels, Aβ oligomers effect neurotoxicity and memory impairments at low nanomolar concentrations [58]. Therefore, residual levels of Aβ production may be sufficient for continued Aβ oligomer-mediated toxicity.

3. Lipid Raft Components Promote Aβ Oligomerisation

3.1. Aβ Oligomers Are the Major Neurotoxic Species in AD. The Aβ peptide is natively unfolded and, under certain conditions, it aggregates to form a heterogeneous mixture of soluble oligomers, protofibrils and fibrils. It was accepted for a long time that the Aβ fibrils that deposit in neuritic plaques, which are observed *post mortem* in diseased brains, were responsible for neurotoxicity in AD [59]. Aβ fibrils have been reported to induce neuronal dysfunction and

cell death, although fibrils are less potent neurotoxins than soluble forms of Aβ [60, 61]. Interestingly, fibrils have been found to become more neurotoxic upon fragmentation [62], raising the possibility that soluble species released from fibril ends may underlie their neurotoxicity. A plethora of studies have now demonstrated that levels of soluble Aβ oligomers in the brain correlate much better than plaques or fibrils with AD onset, progression and severity [5, 6, 8, 63, 64]. Within the last fifteen years, a large number of studies from research groups worldwide have reported the existence of many different oligomeric assemblies from various sources, including AD brain and cerebrospinal fluid (CSF) samples, secreted into the conditioned medium of cultured cells or prepared artificially from recombinant or synthetic Aβ peptides [65]. A heterogeneous range of sizes and peptide conformations have been observed among these natural and artificial Aβ oligomers, including dimers and trimers [66, 67], tetramers, hexamers and the dodecameric Aβ*56 [64], globulomers [68], ring-shaped annular protofibrils [69] and higher molecular weight Aβ-derived diffusible ligands (ADDLs) which can comprise hundreds of monomeric subunits [9, 70] (Figure 2). However, despite the disparity in size and source, Aβ oligomers appear to share important functional properties. Notably, both natural and synthetic Aβ oligomer preparations bind to hippocampal neurons and cells of neuronal lineage, causing a loss of dendritic spines, neurotoxicity, the inhibition of long-term synaptic potentiation (LTP: an electrophysiological correlate of learning and memory) and impairments in working memory at nanomolar concentrations [64, 67, 68, 70–73]. The preferential binding and toxicity of Aβ oligomers towards neurons in the hippocampus may explain why Aβ oligomers correlate with AD severity and disease progression [9, 68, 70]. However, the cellular mechanisms by which these effects are modulated remain poorly understood.

3.2. Aβ Oligomerisation Is Modulated by Lipid Raft Components. Aβ is a physiological peptide which is present in the brain tissue and CSF of healthy subjects throughout life, without necessarily causing neurodegeneration [74–76]. Many studies have shown that monomeric, nonaggregated Aβ does not cause the neurotoxic effects that are mediated by Aβ oligomers. In fact, monomeric Aβ has recently been reported to have neuroprotective roles in the brain [77, 78]. The aggregation of Aβ is necessary for its toxicity [79] and the emerging picture is that soluble Aβ oligomers are the proximate neurotoxins in AD [8, 80]. The aggregation of Aβ is therefore a critical step in the development of AD pathogenesis, and one in which lipid rafts appear to play a fundamental role.

Neuronal sensitivity to Aβ-induced toxicity has been found to be dependent upon Aβ binding to the cell membrane [81] and Aβ has been identified in lipid rafts from cultured cells and from human and rodent brains. Soluble Aβ dimers accumulate rapidly, and have been found at elevated levels, in lipid raft fractions isolated from human and transgenic mouse model AD brains [82]. Importantly, Aβ has been shown to accumulate in presynaptic terminals in AD cortex where it colocalises with the lipid raft markers cholesterol and ganglioside GM1 [83]. Taken together, these data suggest that Aβ accumulation and aggregation within lipid rafts may underlie AD neuropathology.

As cholesterol is a major component of lipid rafts, it was postulated to facilitate Aβ oligomerisation on neuronal membranes. The brain is particularly enriched in cholesterol, harbouring over 23% of the body's total complement but comprising only around 2% of total body mass [84]. However, the role of cholesterol in promoting the assembly of Aβ is controversial and conflicting evidence has been presented in recent years. The main difficulty is being able to distinguish between the key role of cholesterol in building the lipid raft domains necessary for Aβ production and the suggested role of cholesterol in promoting Aβ oligomerisation. As discussed previously, raised cholesterol has been linked to AD; is this solely due to an increase in total lipid raft composition of the plasma membrane which increases amyloidogenic processing of APP to yield more Aβ peptide or due to a direct effect on Aβ oligomerisation?

A growing body of evidence suggests that certain components of lipid raft domains may play a much more sinister role in catalysing the conversion of the aggregation-prone Aβ peptide to its neurotoxic, oligomeric states. Cholesterol is known to modulate the interaction of the Aβ peptide with lipid bilayers [85]. Further, Aβ oligomers isolated from AD patients associate with DRMs in a cholesterol-dependent manner, and cholesterol depletion reduces the aggregation of Aβ [86]. It is currently unknown, however, whether this latter effect is due to a direct interaction between Aβ and cholesterol, or due to the overall depletion in lipid raft domains and/or the subsequent change in composition and properties brought on by a reduction in cholesterol. Conversely, a recent study revealed that increasing the level of cholesterol in human neuroblastoma cells actually reduced the ability of synthetic Aβ oligomers to bind [87], in spite of the colocalisation of the Aβ oligomers with the lipid raft component ganglioside GM1. These data agree with the authors' previous finding that an increased level of membrane cholesterol exerts a protective effect against Aβ oligomer toxicity [88]. In the more recent study [89] it was proposed that a fluctuation in cholesterol levels may alter the physical properties of lipid rafts thereby modulating oligomer binding.

Cholesterol can also facilitate Aβ aggregation through the structural modification of other lipid raft components. A recent study using reconstituted membranes revealed a structural role for cholesterol in modulating the conformation of glycosphingolipids. Depending on the type of glycosphingolipid, cholesterol can either facilitate (such as for ganglioside GM1) or inhibit the interaction of Aβ peptides with lipid rafts through fine-tuning of the glycosphingolipid conformation [90]. This reinforces the notion that Aβ binding to, and aggregation upon, neuronal lipid raft domains cannot be ascribed to a single component, but rather that multiple players are likely to be involved.

In fact, mounting evidence suggests that gangliosides within lipid rafts appear to be the main driving force

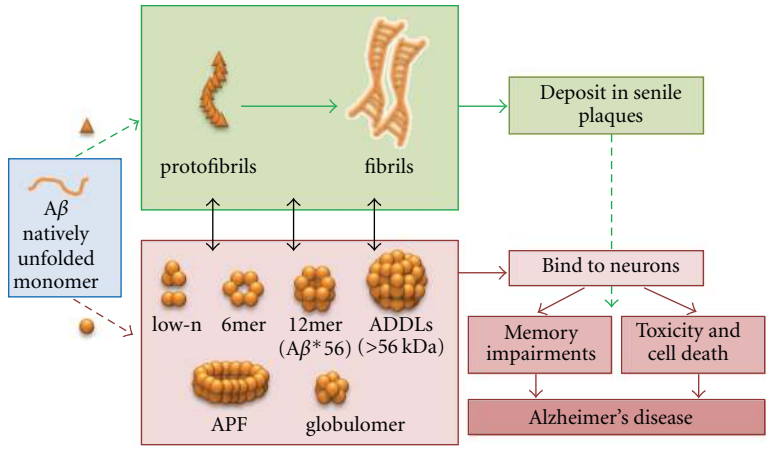


Figure 2: Aβ oligomers are the key neurotoxic assemblies in Alzheimer's Disease. The Aβ peptide is natively unfolded yet conformationally plastic and prone to aggregation. In response to various stimuli, including elevated concentration, Aβ undergoes complex conformational rearrangements to form oligomer-competent or fibril-competent intermediates. A variety of Aβ oligomers can form which include low-n oligomers (dimer and trimers), globulomers, hexameric and dodecameric (Aβ*56) states, higher molecular weight species such as Aβ-derived diffusible ligands (ADDLs) and ring-shaped annular protofibrils (APFs). Some oligomers are stable, off-pathway intermediates whereas others undergo further conformational changes and aggregation to form larger protofibrils and fibrils. Fibrils of Aβ are insoluble and deposit within extracellular senile plaques. Aβ oligomers are soluble and represent the active neurotoxic species in AD. The specific binding of Aβ oligomers to neurons, particularly in the hippocampus, triggers the memory impairments, loss of synaptic functionality and neuronal death which characterise AD.

behind the oligomerisation of Aβ on neuronal membranes. The development of AD within certain brain regions has been found to correlate with increased ganglioside levels [91]. Gangliosides are glycosphingolipids with one or more sialic acid moieties attached to the sugar chain. Gangliosides are found predominantly in the central nervous system, where they are enriched in lipid rafts due to the preferential packing of their saturated acyl chains within the liquid-ordered phase. A study in 1995 revealed that a population of membrane-bound Aβ tightly bound to gangliosides exists in AD brains [92]. More recently, exogenously-applied Aβ was shown to bind to neuronal membranes and to redistribute into lipid rafts where it colocalised with ganglioside GM1 in a time-dependent manner [93]. GM1 facilitated the binding and accumulation of Aβ oligomers at lipid raft domains and appeared to be required for the Aβ oligomer-mediated lipid peroxidation of DRMs [94]. Ganglioside GM1 contains just one sialic acid moiety and plays important physiological roles in neuronal function. Aβ appears to interact with the sialic acid moiety of gangliosides such as GM1 and these bound aggregates can go on to seed further Aβ aggregation [95]. The interaction between sialic acid and Aβ induces a conformational rearrangement of the Aβ peptide chain [96] which may potentiate Aβ oligomerisation. DRMs derived from ganglioside-rich rat brain, but not from liver, were found to promote the oligomerisation of Aβ [97]. Further, this study revealed that the removal of cholesterol or protein from these raft fractions did not prevent Aβ aggregation, providing evidence that neither cholesterol nor protein is essential for this process. However, lipid raft fractions containing very low levels of gangliosides still retained some Aβ oligomerisation ability, and therefore ganglioside-independent aggregation mechanisms cannot be ruled out.

4. Aβ Oligomers Bind to Neuronal Receptors within Lipid Rafts

4.1. Aβ Oligomers Bind to High Affinity Protein Receptors. When the first synthetic Aβ oligomers were prepared from $A\beta_{1-42}$ peptide by the Klein laboratory in 1998, it was observed that their binding to hippocampal neurons and cultured nerve cells was abolished by treating the cells with trypsin [70]. This, coupled with the low oligomer concentration (5 nM) required for neurotoxicity, implied that specific protein receptors were responsible for the binding of Aβ oligomers and for the subsequent transduction and amplification of neurotoxicity. Indeed, a recent study found that Aβ oligomer binding to neurons was saturable with an estimated apparent K_d of ~0.4 nM [9]. This finding implied that one or more high-affinity receptors are responsible for Aβ oligomer binding and subsequent neurotoxicity. Immunofluorescence microscopy has revealed that Aβ oligomers bind to dendritic spines of hippocampal neurons where they colocalise with postsynaptic markers [9, 98, 99]. Interestingly, Aβ oligomer binding to neurons has a punctate appearance [100], which is reminiscent of the appearance of lipid raft localised proteins [101]. Several putative neuronal receptors for Aβ have been identified in recent years, namely proteins that are related to mechanisms of memory and neuroprotection in the brain. Noteworthy, all of these receptors either reside primarily within, or can partition into, lipid raft domains at the surface of neurons. Lipid rafts may therefore hold the key to

understanding how the deleterious effects of Aβ oligomers are transduced through binding to specific receptors within these microdomains.

4.2. The Cellular Prion Protein (PrP^{Sc}). In 2009, Laurén and colleagues reported that the cellular prion protein (PrP^{C}) is a specific, high-affinity neuronal receptor for Aβ_{1-42} oligomers [9]. PrP^{C} is a GPI-anchored protein that is expressed at high levels in the brain, particularly at synapses and axons, where it resides in lipid rafts. The misfolded form of the prion protein (PrP^{Sc}) is infamous for being the causative agent in Mad Cow Disease (Bovine Spongiform Encephalopathy, BSE) and its human equivalent, Creutzfeldt-Jakob Disease (CJD). Although the correctly-folded PrP^{C} is critical for prion disease pathogenesis, its physiological function remains enigmatic, with potential neuroprotective roles in oxidative stress defence, metal ion homeostasis and anti-apoptosis [102]. In a search to identify neuronal receptors for Aβ oligomers, Laurén et al. [9] screened a mouse brain expression library of 225,000 cDNA constructs from which only two positive clones, both encoding full-length PrP^{C}, were isolated that were able to bind Aβ oligomers with high affinity and specificity. Interestingly, the PrP^{C} homologues Shadoo and Doppel were found not to bind Aβ oligomers to any significant degree. A further, more focussed screen of 352 clones encoding transmembrane proteins identified amyloid-β precursor-like protein 1 (APLP1) and transmembrane protein 30B (TMEM30B) as weak Aβ receptors, although their specificity for oligomeric Aβ was poor. The α7 nicotinic acetylcholine receptor (nAChRα7) and the receptor for advanced glycation end products (RAGE) were also assayed due to their previously reported affinities for Aβ peptides [103, 104], although neither displayed high-affinity Aβ oligomer binding. Therefore, PrP^{C} was the only identified receptor to display both high affinity and high specificity for Aβ oligomers.

A direct interaction between PrP^{C} and Aβ oligomers was confirmed and the core oligomer binding region of PrP^{C} was narrowed down to amino acids 95–110, a positively charged cluster rich in lysine residues [9]. PrP^{C} was also shown to mediate the inhibition of LTP that is induced when hippocampal slices were incubated with Aβ oligomers at nanomolar concentrations [9]. A follow-up *in vivo* study revealed that the presence of PrP^{C} is required for the Aβ oligomer-mediated memory impairments in an AD model mouse [105]. Taken together, these data indicate a strong association between Aβ oligomers binding to PrP^{C} within lipid rafts of hippocampal neurons and the induction of memory deficits that are characteristic of AD.

Nevertheless, there has been some dispute over the role of PrP^{C} in transducing the deleterious effects of Aβ oligomers *in vivo*, as other studies have reported data which oppose this theory. First, Balducci and colleagues reported that although Aβ oligomers bind tightly to PrP^{C} they cause impairments in long-term memory in mice independently of PrP^{C} [106]. In this study, the effects of synthetic Aβ oligomers upon wild-type mice were observed, whereas Gimbel et al. [72] utilised a mouse model expressing a familial AD mutant APP. Further, the synthetic depsipeptide and the oligomer preparation method utilised by Balducci et al. [106] differed from those used by Gimbel and coworkers [72], raising the possibility that PrP^{C} does not have the same binding affinity for all types of Aβ oligomers. Second, the Aguzzi group crossed an AD mouse model, which suffers from Aβ-dependent memory deficits in the form of LTP impairment, with mice expressing either wild-type PrP^{C}, a secreted form of PrP^{C} (lacking its GPI anchor) or no PrP^{C} [107]. They found that the presence or absence of wild-type PrP^{C} had no effect upon the Aβ-mediated inhibition of LTP. However, expression of the secreted form of PrP^{C} was found to suppress the impairment in LTP, which the authors proposed may be due to the potential chelation and subsequent degradation of Aβ oligomers by soluble PrP^{C} in the extracellular milieu. Third, Kessels and coworkers reported the influence of PrP^{C} upon hippocampal neurons expressing a C-terminally truncated form of APP in a viral expression construct [108]. The same loss of dendritic spines and inhibition of LTP were observed in the presence and absence of PrP^{C}, suggesting that Aβ-mediated synaptic defects do not require PrP^{C}. However, Laurén and colleagues have emphasised the differences in the model system utilised by Kessels and coworkers in their study which may account for the opposing data, namely the viral expression of APP, a higher concentration of Aβ oligomers and a difference in the observed suppression of synaptic plasticity [109].

Further investigation is needed to clarify the role of PrP^{C} in modulating the Aβ oligomer-mediated impairments in memory and LTP. Differences in the oligomer preparations, age and genotype of the mouse models, the nature of the promoter elements driving gene expression and the particular memory tests employed by the different authors may account for the discrepancies in the data.

The binding of Aβ oligomers to PrP^{C} is not the first time that PrP^{C} has been linked to AD. Senile plaques from a subset of AD patients were observed to contain PrP^{C} [110] and abundant Aβ deposits have been observed in some CJD cases [111]. Furthermore, the Met/Val 129 polymorphism in the *PRNP* gene that encodes PrP^{C} is a risk factor for early-onset AD [112]. In 2007, we demonstrated that PrP^{C} negatively modulates Aβ production through inhibition of the APP cleaving enzyme, BACE1 [113]. These data, along with the recent discovery that PrP^{C} binds to Aβ oligomers and transduces their deleterious effects, raises the intriguing possibility of a feedback loop [114]. We propose that, physiologically, PrP^{C} maintains Aβ production at a low level through BACE1 inhibition, but in AD this interaction may be disrupted by Aβ oligomers binding to PrP^{C} and causing its segregation from BACE1. Therefore, Aβ oligomers binding to PrP^{C} may also promote their own production through the ablation of BACE1 inhibition by PrP^{C}. More recently, levels of PrP^{C} have been shown to be reduced in AD brains [115, 116] possibly arguing against PrP^{C} being involved in mediating the neurotoxic effects of Aβ oligomers, at least in the terminal stages of the disease.

It is important to note that Laurén and colleagues reported that the removal of PrP^{C} from hippocampal neurons only reduced Aβ oligomer binding by approximately

50% [9]. This suggests that other receptors not identified in the expression library screen due to nonpreferential binding conditions or a low affinity for the particular type of Aβ oligomers that were used, and/or nonprotein lipid raft components, may play equally crucial roles in Aβ oligomer binding and neurotoxicity. Glutamate receptors, which possibly exist in a complex with PrP^C [117], represent a candidate interacting partner for Aβ oligomers which could explain the deleterious effects upon hippocampal synaptic plasticity.

4.3. Glutamate Receptors. Synaptic failure and impairments in synaptic plasticity are hallmarks of early AD neuropathology [100, 118, 119]. LTP and long-term depression (LTD) are mechanistic dimmer switches which facilitate synaptic plasticity by strengthening or weakening communication across a synapse, respectively, with LTP being essential for hippocampal-dependent learning and memory [120, 121]. Numerous lines of study have confirmed that soluble Aβ oligomers from various sources, including those isolated from AD brains, disrupt hippocampal LTP *in vitro* and *in vivo* and cause impairments in learning and memory [9, 67, 70, 107, 122, 123]. Although not all studies agree, it has also been demonstrated that Aβ oligomers can provoke LTD which opposes LTP [67, 124, 125]. Neuronal receptors which modulate LTP and/or LTD are therefore likely candidates for the specific binding of Aβ oligomers. Glutamate receptors are central to the modulation of LTP and LTD. Additionally, glutamate receptor dysfunction has been implicated in AD which is characterised by memory deficits caused by impaired synaptic plasticity [126]. Glutamate receptors consist of two classes; ionotropic (cation-specific ion channels) and metabotropic (G-protein-coupled). Members of both classes have been implicated as neuronal receptors for Aβ oligomers.

4.3.1. NMDA Ionotropic Glutamate Receptors. N-methyl-D-aspartate receptors (NMDARs) constitute a major class of glutamate receptors in the mammalian brain which localise to the postsynaptic membrane of excitatory synapses [127]. These ion channels play key roles in excitatory synaptic transmission and synaptic plasticity [128]. The membrane channel is usually blocked by Mg^{2+} ions which are displaced when synaptic transmission results in depolarisation and glutamate release and binding. NMDAR channel opening leads to the rapid influx of Ca^{2+} which triggers LTP induction [129]. Longer-term effects which maintain the reinforced synapse include the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), altered gene expression and kinase activity and the growth of new dendritic spines. Interestingly, NMDAR activation can also stimulate LTD, having the opposing effect of synapse weakening, and this appears to depend upon the nature of the stimulus and the subtype of NMDAR involved [130].

NMDARs localise to lipid raft domains where they interact with flotillins [131, 132] although they can move laterally between raft and nonraft domains in response to cues including phosphorylation [133]. Statins, which deplete cellular cholesterol thus reducing lipid raft formation, have been shown to reduce the localisation of NMDARs to lipid raft domains, which has a neuroprotective effect [134].

Mounting evidence points towards a central role for NMDARs in the modulation of Aβ oligomer toxicity. Soluble Aβ oligomers inhibit NMDAR-dependent LTP [70, 135] and exhibit postsynaptic binding to hippocampal neurons which express NMDAR subunits GluN1 and GluN2B [100]. A reduction in NMDAR subunits GluN1 and GluN2B has previously been observed in the hippocampus of AD brains [136]. Crucially, a recent study has confirmed that Aβ oligomer-mediated early synaptic dysfunction depends upon the activation of GluN2B-containing NMDARs [10]. Aβ oligomers were found to decrease the NMDAR-dependent influx of Ca^{2+} into dendritic spines [137], and to reduce dendritic spine and synapse density [10] in a mechanism which involve the subsequent phosphorylation of tau [138]. NMDAR antagonists, including one which is specific for GluN2B subunits, were able to reverse the Aβ-induced loss of dendritic spine density [100, 137, 139]. These effects are consistent with Aβ oligomers blocking the NMDAR-mediated stimulation of LTP whilst promoting NMDAR-mediated LTD. In addition, Aβ oligomers have been shown to stimulate the excessive generation of reactive oxygen species (ROS) through an NMDAR-dependent mechanism [140], suggesting a link between aberrant ROS regulation and Aβ-induced cognitive impairment.

Furthermore, evidence to confirm a direct interaction between Aβ oligomers and NMDAR subunits has recently been presented. Partial colocalisation was observed between NMDAR GluN2B and Aβ oligomers in hippocampal slices, which increased upon the addition of glutamate, although the maximum colocalisation was less than 50% [141]. Further, Aβ oligomers were recently found to coimmunoprecipitate with NMDAR subunits [117]. However, an indirect model proposed by Venkitaramani and colleagues suggests that the Aβ oligomer-mediated decrease in GluN2B-containing NMDARs results from the former binding to α-7 nicotinic acetylcholine receptors (α7nAChR), which activates striatal-enriched tyrosine phosphatase (STEP), in turn stimulating NMDAR internalisation [142]. More recent data has revealed elevated levels of STEP in a mouse model of AD and in human AD brains, and that the removal of STEP abrogates the Aβ-mediated reduction in NMDARs at the cell surface [143]. Whether or not Aβ oligomers interact with NMDARs directly, growing evidence suggests that NMDARs play an important role in transducing the deleterious effects of Aβ oligomers upon synaptic functionality.

4.3.2. mGluR5 Metabotropic Glutamate Receptor. The mGluR5 metabotropic glutamate receptor plays important regulatory roles in neuronal calcium mobilisation and the modulation of LTP and excitatory postsynaptic potentials in hippocampal neurons [144, 145]. Recently, mGluR5 was identified as a novel Aβ oligomer receptor in a study of the behaviour of fluorescently-labelled Aβ oligomers on hippocampal neurons and their interaction with neuronal receptors [117]. The Aβ oligomers bound to excitatory

synapses where their mobility decreased as they aggregated to form larger clusters over time. Consistent with previous data, Aβ oligomers caused a removal in NMDARs from synapses and were found to coimmunoprecipitate with NMDAR subunits. Interestingly, the Aβ oligomers also formed complexes with mGluR5 receptors, which caused their lateral redistribution into dendritic spines followed by Ca^{2+} dysregulation. Renner and colleagues also observed a time-dependent increase in lipid raft-localised mGluR5s which suggests that Aβ oligomers reduce the mobility of mGluRs, causing their aberrant aggregation within pathological signalling platforms [117]. When mGluR5 was removed from mouse hippocampal neurons, Aβ oligomer binding was reduced by approximately 80% and the loss of NMDARs from the cell surface was prevented.

Metabotropic glutamate receptors have been implicated previously in the pathogenesis of AD and other neurodegenerative disorders [126]. Impaired mGluR signalling in the cortex of AD patients has been shown to correlate with AD-related neuropathological changes [146]. Interestingly, the stimulation of mGluRs can modulate APP processing [147]. A recent study revealed that the Aβ peptide upregulates the expression of mGluR5s in astrocytes, protective nonneuronal cells which are implicated in AD pathogenesis and inflammation [148]. Increased levels of mGluR5s were observed in the brains of Down's syndrome patients [149]; a disease in which elevated levels of Aβ result from the triplication of the APP gene [150].

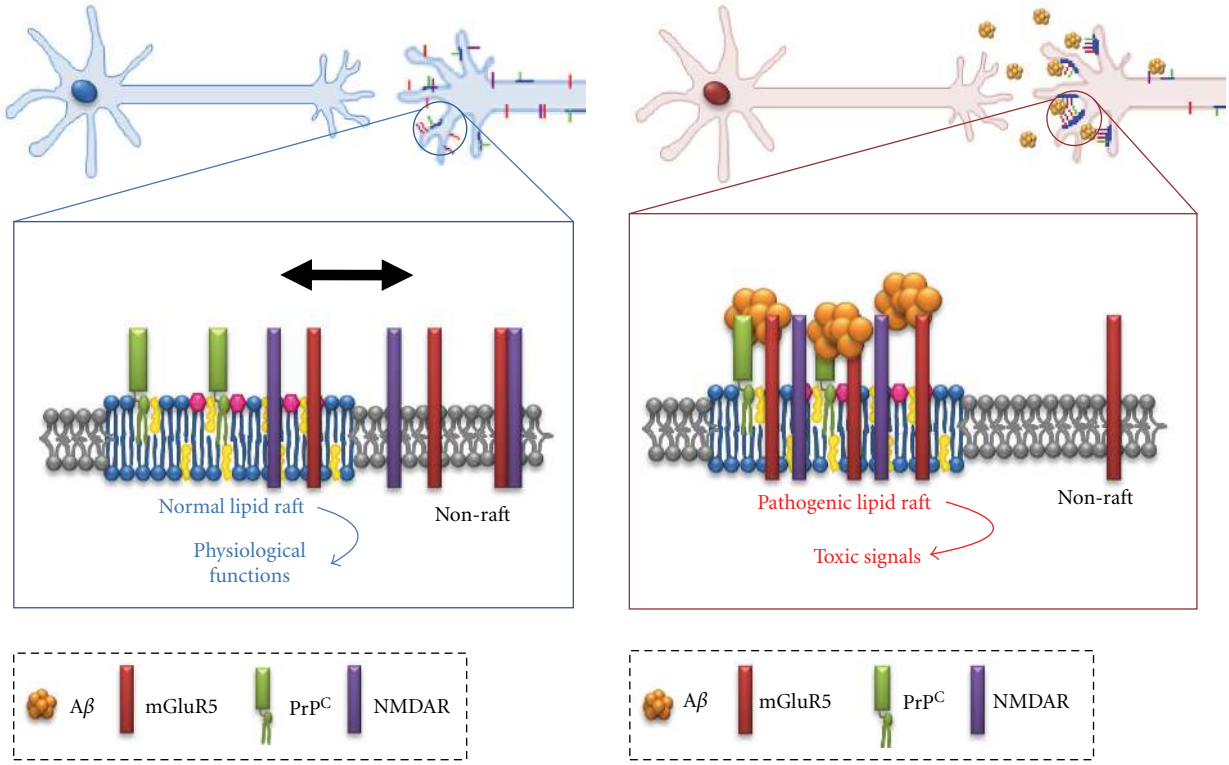
4.3.3. Other Putative Receptors. Various other lipid raft-associated proteins have been reported to effect Aβ-mediated synaptic dysfunction. For instance, the removal of nerve growth factor receptors (NGFRs), including TrkA and p75 neurotrophin receptor, from cells treated with GM1-induced Aβ oligomers caused a significant reduction in oligomer-mediated cytoxicity [151]. NGFR dysfunction and aberrant NGF signalling is associated with AD and increased Aβ production [152, 153]. Although no direct interaction has been shown to our knowledge, it is possible that interplay between Aβ oligomers and NGFRs may form part of a positive feedback loop which serves to reinforce Aβ oligomer production, whilst blocking NGF signalling with deleterious effects upon neuronal survival. Physiologically, NGF binds to TrkA causing the translocation and clustering of receptors within lipid rafts [154]. The binding of Aβ oligomers to TrkA and other NGFRs may therefore cause aberrant lipid raft clustering which prevents or disrupts the formation of the normal signalling platforms.

Recent research proposes that impaired insulin signalling may be involved in AD, even leading to the hypothesis that AD represents a third type of diabetes [155]. Insulin receptors, which are robustly expressed in hippocampal neurons, were found to bind Aβ oligomers and to undergo internalisation from dendritic spines [156]. Perturbations in insulin signalling in the brain caused by Aβ oligomers may impair memory and LTP [157]. Interestingly, insulin receptor subunits are also enriched in lipid raft domains in hippocampal neurons [158].

4.3.4. Multireceptor, Pathogenic Signalling Platforms Are Induced by Aβ Oligomers. The emerging picture is that lipid rafts accommodate multiple receptors for Aβ oligomers, namely PrP^C along with NMDAR, mGluR5 and possibly other, lower affinity receptors. Interestingly, there is evidence to suggest that these three lipid raft-associated receptors interact together. Metabotropic glutamate receptors have been found to cocluster with NMDARs [159]. It has also been reported that PrP^C inhibited NMDAR function in hippocampal neurons and coimmunoprecipitated with NMDAR subunits [160]. The functional and physical links between these Aβ oligomer receptors suggest the existence of a multi-component, Aβ oligomer binding raft complex, comprising of PrP^C, mGluR5 and NMDAR (Figure 3) [117]. Whether the formation of this complex is required for oligomer binding, or whether the interaction of Aβ oligomers with the individual proteins induces its assembly, is a "chicken and egg" situation. One possible hypothesis is that Aβ oligomers promote the clustering of PrP^C and glutamate receptors into pathological mega-scaffolds which induce both toxic loss- and gain-of-function downstream effects. For instance, the aberrant localisation of glutamate receptors may impede neuronal signalling mechanisms including LTP, while the clustering or internalisation of NMDARs may promote their LTD-inducing functionality. The combined effects of oligomer binding upon more than one glutamate receptor is likely to be a large disturbance in Ca^{2+} homeostasis which results in pathological signalling cascades. Interestingly, the PrP^C-mediated response to oxidative stress is thought to induce signalling cascades which can modulate Ca^{2+} flux and synaptic plasticity [161]. Furthermore, Aβ oligomers may cause the internalisation or loss of function of components such as PrP^C thus reducing neuroprotection against oxidative stress at the cell surface. The clustering of Aβ oligomers at lipid raft domains may also cause damage to physiologically important signalling rafts, thus impairing neuronal function. Furthermore, the Aβ oligomer-induced redistribution of neuronal proteins into lipid rafts may influence their nonraft interacting partners, with additional deleterious effects upon neuronal function and integrity.

5. Conclusions

Neuronal lipid rafts are crucial modulators of Aβ production and aggregation, leading to the accumulation of neurotoxic Aβ oligomers in the brain which drive AD pathology. Recent evidence now incriminates lipid rafts as pathological signalling platforms in which Aβ oligomer receptors, such as PrP^C and glutamate receptors, cluster. Aβ oligomer binding appears to induce the aberrant localisation of these proteins with deleterious effects upon their physiological functions including hippocampal LTP, which underlies memory, and defence against oxidative stress. In this way, lipid rafts appear to be directly responsible for the transduction of Aβ oligomer-mediated memory impairments and neurotoxicity which characterise AD. Lipid rafts are not only implicated in AD but may also be the key to a range of neurodegenerative



(a) Normal (b) Alzheimer's disease

Figure 3: Aβ oligomer binding stimulates the clustering of specific neuronal receptors into aberrant pathogenic signalling platforms at the synapse. (a) Synaptic function and neural communication is maintained by the activity of postsynaptic receptors including the neuroprotective PrP^C and the NMDA and mGluR5 glutamate receptors, which modulate synaptic plasticity. In the healthy brain, the dynamic translocation of such receptors between lipid raft and nonraft domains of the plasma membrane modulates their activities; (b) in AD, the binding of Aβ oligomers at postsynaptic membranes causes the redistribution and clustering of receptors including PrP^C, NMDAR and mGluR5 into pathological signalling platforms [117]. The resulting loss of transient lateral movement and subsequently interaction with other components is proposed to cause a loss of normal functionality combined with aberrant signalling by these receptors. The dysregulation of $Ca2^+$ and inhibition of synaptic long-term potentiation likely underlie the memory deficits which characterise AD. Further, the loss of PrP^C depletes neuronal protection against oxidative stress which may partially account for the neuronal death that is observed in AD brains.

proteinopathies, including Parkinson's Disease, Huntington's Disease, amyotrophic lateral sclerosis and prion diseases (reviewed in [12]). Indeed, lipid raft disruption protects neurons against the toxicity of other oligomers besides Aβ [22] and lipid rafts may therefore represent generic platforms for oligomer-mediated neurotoxicity. Understanding the cell biology of the downstream effects of amyloid oligomers binding to neuronal lipid raft proteins may uncover potential therapeutic targets for the prevention of AD and other neurodegenerative diseases.

Abbreviations

α7nAChR: α-7 nicotinic acetylcholine receptor
Aβ: Amyloid-beta
AD: Alzheimer's Disease
ADDL: Aβ-derived diffusible ligand
AICD: APP intracellular domain
AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
APF: Annular protofibril
APH1: Anterior pharynx defective-1
APLP1: Amyloid-β precursor-like protein 1
APP: Amyloid precursor protein
BACE1: Beta-site APP cleaving enzyme-1
BSE: Bovine Spongiform Encephalopathy
CJD: Creutzfeldt-Jakob Disease
CSF: Cerebrospinal fluid
DRM: Detergent-resistant membrane
GPI: Glycosyl phosphatidylinositol
K_d: Apparent dissociation constant
LTD: Long-term synaptic depression
LTP: Long-term synaptic potentiation
mGluR: Metabotropic glutamate receptor
NGFR: Nerve growth factor receptor
NMDAR: N-methyl-D-aspartate receptor
PEN2: Presenilin enhancer-2
PrP^C: Cellular isoform of the prion protein
PrP^{Sc}: Scrapie isoform of the prion protein

RAGE: Receptor for advanced glycation end products
STEP: Striatal-enriched tyrosine phosphatase
TMEM30B: Transmembrane protein 30B.

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