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Review

Amyloid β-Peptide Interactions with Neuronal and Glial Cell Plasma Membrane: Binding Sites and Implications for Alzheimer's Disease

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Abstract: The extracellular accumulation of amyloid-beta (Aβ) in neuritic plaques is one of the characteristic hallmarks of Alzheimer's disease (AD), a progressive dementing neurodegenerative disorder of the elderly. By virtue of its structure, Aβ is able to bind to a variety of biomolecules, including lipids, proteins and proteoglycans. The binding of the various forms of Aβ (soluble or fibrillar) to plasma membranes has been studied with regard to the direct toxicity of Aβ to neurons, and the activation of a local inflammation phase involving microglia.

The binding of Aβ to membrane lipids facilitates Aβ fibrillation, which in turn disturbs the structure and function of the membranes, such as membrane fluidity or the formation of ion channels.

A subset of membrane proteins binds Aβ. The serpin-enzyme complex receptor (SEC-R) and the insulin receptor can bind the monomeric form of Aβ. The α7nicotinic acetylcholine receptor (α7nAChR), integrins, RAGE (receptor for advanced glycosylation end-products) and FPRL1 (formyl peptide receptor-like 1) are able to bind the monomeric and fibrillar forms of Aβ. In addition, APP (amyloid precursor protein), the NMDA-R (N-methyl-D-aspartate receptor), the P75 neurotrophin receptor (P75NTR), the CLAC-P/collagen type XXV (collagen-like Alzheimer amyloid plaque component precursor/collagen XXV), the scavenger receptors A, BI (SR-A, SR-BI) and CD36, a complex involving CD36, $\alpha_6\beta_1$–integrin and CD47 have been reported to bind the fibrillar form of Aβ.

Heparan sulfate proteoglycans have also been described as cell-surface binding sites for Aβ. The various effects of Aβ binding to these membrane molecules are discussed.

Keywords: amyloid-beta; Alzheimer's disease; membrane proteins; membrane lipids

Abbreviations: α7nAChR, α7 nicotinic acetylcholine receptor; Aβ, amyloid-beta; AD, Alzheimer's disease; ApoA, apolipoprotein A; ApoE, apolipoprotein E; ApoJ, apolipoprotein J; APP, amyloid precusor protein; BBP, β-amyloid binding protein; CHO, Chinese hamster ovaries; CLAC-P/Col XXV, collagen-like Alzheimer amyloid plaque component precursor/collagen XXV; CR3, complement receptor 3; CSF, cerebrospinal fluid; fAβ, fibrillar amyloid-beta; FPRL1, formyl peptide receptor-like 1; HDL, high density lipoprotein; HSP, heparan sulfate proteoglycan; IL, interleukin; LRP, low-density lipoprotein receptor-related protein; M-CSF, macrophage-colony stimulating factor; NFKB, nuclear factor kappa B; NMDA, N-methyl-D-aspartate receptor; P75NTR, P75 neurotrophin receptor; RAGE, receptor for advanced glycosylation end-products; ROS, reactive oxygen species; SEC-R, serpin complex receptor; serpin, serine proteinase inhibitor; sGAG, sulfated glycosaminoglycans; SR-A, scavenger receptor A; SR-BI, scavenger receptor BI.

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive and irreversible decline of cognitive function. A majority of AD is sporadic, although several genetic linkages have also been identified.

A prominent feature of AD is the extracellular accumulation of amyloid-beta (Aβ) in neuritic plaques. Aβ is a 37–43 -amino acid peptide (Figure 1) that derives from multiple proteolytic cleavage of a large transmembrane precursor, the amyloid precursor protein (APP) [1].

It is widely accepted that AD syndrome starts with various gene defects, leading to altered APP expression or proteolytic processing, or to changes in Aβ stability or aggregation. These in turn result in a chronic imbalance between Aβ production and clearance. Aβ is released extra- and intracellularly, and can also be accumulated extra- and intracellularly. The gradual accumulation of aggregated Aβ may initiate a complex, multistep cascade that includes gliosis, inflammatory changes, neuritic/synaptic changes, the formation of neurofibrillary tangles and transmitter loss (for reviews, see [2–4]).

The aggregation of physiologically secreted soluble Aβ to oligomers and large Aβ fibrils is currently considered to be a crucial event in AD. A model involving a conformational change from an α-helix or random coil to a β-sheet structure has been proposed (for a review, see [5]). Fibril formation is a multistep process (Figure 2), comprising an initial nucleation step, which is rate limiting, and results in small oligomers (dimers, trimers to dodekamers) followed by a rapid fibril elongation stage to protofibrils and fibrils. Aβ has been found to have surfactant qualities in a surface tension study, and it has been suggested that above a critical Aβ concentration of 0.1 mM, the nucleation event is a result of Aβ micelle formation [6]. The micelles self-associate and collapse to form a dense nucleus, or can associate on a preformed seed. Fibril elongation initially occurs via the formation of

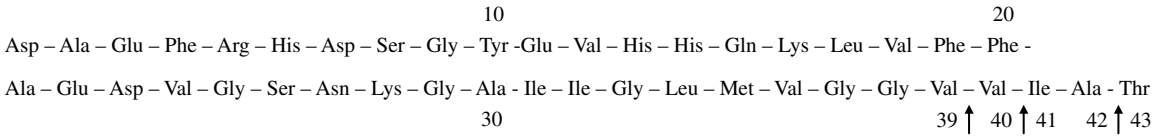

Figure 1 The amino acid sequence of β-amyloid peptides (Aβ_{1-39}, Aβ_{1-40}, Aβ_{1-42} and Aβ_{1-43}).

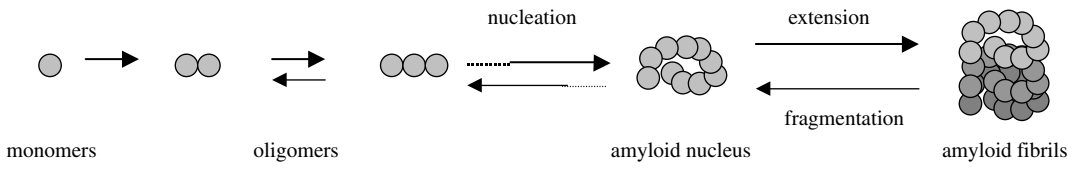

Figure 2 Aggregation of β-amyloid is a multistep process.

small intermediate species that are toxic to cultured neurons [7]. The toxicity of these early aggregates appears to result from an intrinsic ability to impair fundamental cellular processes by interacting with cellular membranes, causing oxidative stress and increasing free Ca^{2+} that eventually lead to apoptotic or necrotic cell death [8]. Protofibrils associate laterally to form amyloid fibrils (for a review, see [9]). It is possible that the fibril itself may be protective; fibrillization would be an efficient way for the cell to sequester potentially toxic protofibrils [10]. However, the association of amyloid fibril formation with toxicity in AD make this theory appear unlikely [4,9,11], even if the mature amyloid fibrils or plaques appear now to be substantially less toxic than the pre-fibrillar aggregates [8]. Recent data have shown that major Aβ species (>60%) found in Aβ aggregate at the earliest stages of Aβ pathology were amino-truncated $A\beta_{x-42}$ [12]. According to recent opinions, AD begins with subtle alterations of hippocampal synaptic efficacy prior to neuronal degeneration, and this synaptic dysfunction is caused by diffusible oligomeric assemblies of Aβ [3,13–18].

A trophic effect of the low-dose monomer has been suggested in many different systems beginning with Cotman's initial report on cultured neurons [19]. These trophic properties emanate from the protein's ability to capture redox metal ions (Cu, Fe) and also Zn, thereby preventing them from participating in redox cycling with other ligands. The chelation of Cu by Aβ would therefore be predicted to dampen oxidative stress in the mildly acidic and oxidative environment that accompanies acute brain trauma and AD. Given that oxidative stress promotes Aβ generation, the formation of diffuse amyloid plaques is likely to be a compensatory response for removing reactive oxygen species. This 'chameleon' property of Aβ should be considered for the development of therapeutics targetted at removal of Aβ from the brain [20].

Aβ oligomers and protofibrils have been implicated in neurotoxicity through their direct action on neuronal cells. However, neurotoxicity can also be induced indirectly by glial cells, since fibrillar Aβ (fAβ) (but not nonfibrillar Aβ) has been shown to trigger glial cells to produce toxic mediators, ultimately leading to the progressive neurodegeneration associated with AD. Immune regulation by fAβ is a key event that initiates the inflammatory cascade at the site of fAβ deposition that contributes to the pathogenesis of AD ([21,22], and for reviews see [3,23]).

The binding of Aβ to the plasma membranes is a potential point of intervention in the events leading to the development of AD, although the view is emerging that a toxic intracellular $A\beta_{1-42}$ accumulation can be detected in neurons before extracellular Aβ deposits (for a review, see [24]). The binding of Aβ to the membranes has been studied with regard to the direct toxicity of Aβ on neurons, and the activation of a local inflammation phase involving microglia. This review focuses on the membrane sites that may mediate the interaction between Aβ and the plasma membranes.

INTERACTION OF Aβ WITH LIPIDS

By virtue of its structure, Aβ is able to bind a variety of lipids (Figure 3).

Aβ, Apolipoproteins and High-density Lipoprotein

The binding of soluble Aβ to normal human plasma high-density lipoprotein (HDL), including apolipoprotein A (ApoA) -I, ApoA-II, apolipoprotein E (ApoE) and apolipoprotein J (ApoJ) has been demonstrated [25]. Apolipoproteins are part of the lipoprotein complex that transports lipids, including cholesterol. ApoE-4, a cholesterol transport protein has been proposed to be a risk factor for late-onset development of AD [26,27], but its role in the disease is poorly understood. ApoE binds Aβ peptides and is believed to promote fibrillization of soluble Aβ, affecting amyloid clearance from the brain [27,28]. The importance of ApoE in Aβ deposition has been strongly suggested in ApoE-knockout mice, where there is markedly decreased Aβ deposition and little or no fibrillar Aβ [29].

Protein-free HDL lipid particles bind Aβ peptide and inhibit aggregation, as does intact HDL. Aβ association with lipoproteins inhibits neurotoxicity by maintaining Aβ solubility in body fluids [30–32]. More recent studies have shown that soluble Aβ associates with HDLs in the central nervous system, cerebrospinal fluid (CSF) and normal blood [33]. Studies on AD of CSF-HDL subfractions by sodium dodecyl sulfate/polyacrylamide gel electrophoresis and immunoblot analysis after CSF fractionation via density flotation ultracentrifugation demonstrated that the CSF in cases of AD was characterized by (i) an increased Aβ and Apo content of HDL(1) and (ii) soluble Aβ association with ApoE and ApoJ in HDL(2), HDL(3) and very high density lipoproteins. This finding supports the hypothesis

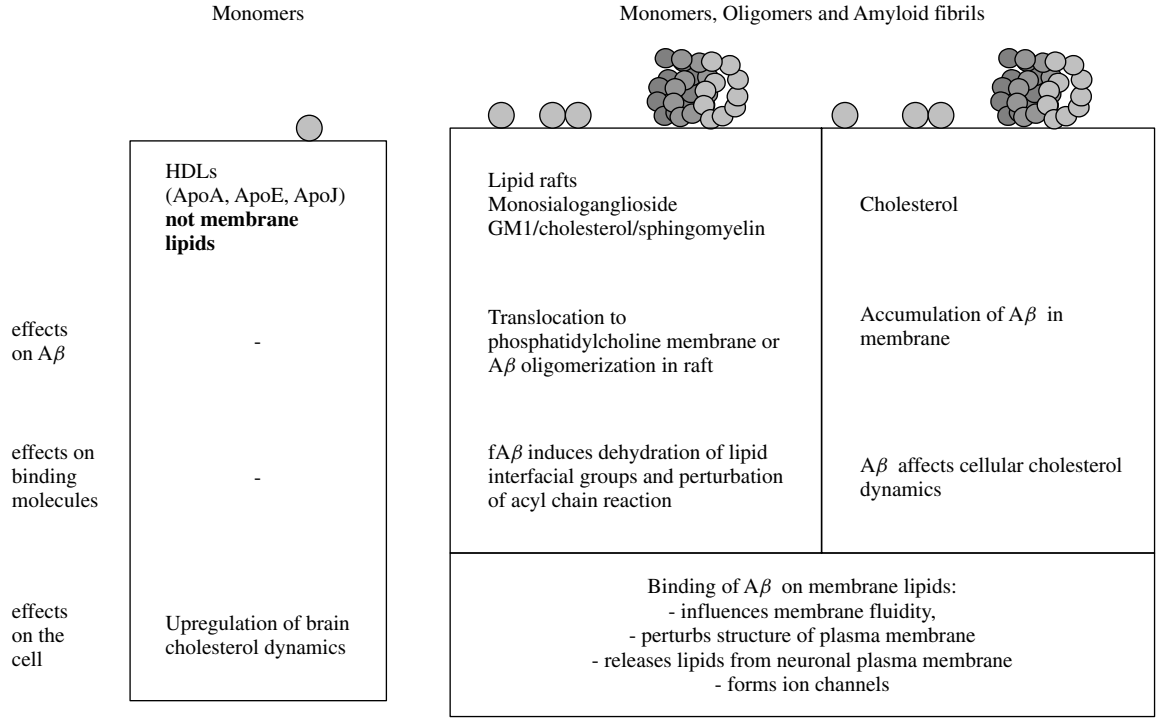

Figure 3 Different forms of β-amyloid interact with lipids.

that upregulation of brain cholesterol dynamics is a fundamental event in the pathophysiology of AD and that binding of Aβ to apolipoproteins and lipids may have important structure–functional consequences [33].

Interaction of Aβ with Lipid Membranes

Lipids are essential for the structural and functional integrity of the membranes. Membrane lipids are not randomly distributed but are localized in different domains, which are the exofacial and cytofacial leaflets, cholesterol pools, annular lipids and lipid rafts. Membrane lipid domains have been proposed to be involved in a variety of different functions including signal transduction, lipid transport and metabolism and cell growth.

Generalities about the interactions of Aβ with lipid membranes. Aβ is known to interact with the cell membrane and also with the membranes of subcellular organelles (lysosome, Golgi complex and endoplasmic reticulum). In consequence of its lipophilicity, Aβ can interact strongly with the lipid bilayer [34], leading to an increase in Aβ fibrillogenesis and modifications of bilayer properties. The size of the Aβ aggregate and its hydrophobicity have been correlated with a decrease of membrane fluidity [35]. Self-association of Aβ into aggregates exposes hydrophobic sites and induces a change in model membrane fluidity. Both soluble and aggregated $A\beta_{1-40}$ significantly increased the synaptic plasma membrane bulk and protein annular fluidity [36]. Aβ fibrillogenesis was accelerated in the presence of plasmal lysosomal and endosomal membranes, and $A\beta_{1-40/42}$ decreased the fluidity of the fatty acyl and head groups of these membranes, which is consistent with Aβ insertion into the bilayer. In contrast, the interaction between $A\beta_{1-40/42}$ and the Golgi bilayer membrane did not enhance Aβ fibrillogenesis, and it increased the Golgi membrane fluidity [37].

Aβ and lipid rafts. Aβ fibrillogenesis has been proposed to take place in lipid rafts of the membrane containing a ganglioside cluster. Formation of ganglioside clusters is facilitated by cholesterol, and Aβ displays a specific affinity to cholesterol [38]. After binding to raft-like membranes composed of monosialoganglioside GM1/cholesterol/sphingomyelin (1/1/1), the Aβ peptide can translocate to the phosphatidylcholine membranes. This translocation process competes with the oligomerization of the peptide in the raft-like membranes. The lipid rafts containing a ganglioside cluster may serve as a conformational

catalyst or a chaperone, generating a membrane-active form of Aβ with seeding ability [39]. Furthermore, it has been established by Fourier transform infrared-polarized attenuated total reflection that fAβ_{1-40} forms an antiparallel beta-sheet on the membrane. The plane of this beta-sheet lies parallel to the ganglioside-containing membrane surface, inducing dehydration of the lipid interfacial groups and perturbation of the acyl chain orientation [40]. Other literature data also support the theory that Aβ-peptides bind to gangliosides in membranes, and this binding enhances peptide fibril formation [41,42], suggesting a mechanism whereby Aβ-peptide induces membrane damage [43]. Aβ undergoes a conformational transition upon interaction with sphingolipids; the Aβ peptide interacts with sphingomyelin via V3-like domains [44]. Thus, sphingomyelin may facilitate the adoption of pathogenic fibril-forming conformations of Aβ peptides. Aβ has been shown to disrupt membrane signal transduction processes present in sphingomyelin-containing lipid rafts. For example, Aβ impaired the coupling of muscarinic cholinergic receptors, metabotropic glutamate receptors and thrombin receptors to the GTP-binding protein Gq 11 [45–47].

In conclusion, the binding of Aβ to the lipid membranes facilitates fAβ formation, which in turn disturbs the structure and function of the membranes.

Aβ and cholesterol. There is a growing body of evidence showing an association between cholesterol and AD (for a review, see [48]). An inverse correlation between membrane cholesterol level and binding of Aβ to cell surface, and subsequent cell death, has been established by fluorescence microscopy. These results suggest that interactions between Aβ and cell surface are mediated by the cellular cholesterol levels, the distribution of cholesterol throughout the cell and membrane fluidity [49]. Moreover, it has been suggested that changes with age in the asymmetric distribution of cholesterol in contrast to total or bulk cholesterol in neuronal plasma membranes provide a cooperative environment for the accumulation of Aβ in plasma membranes, this accumulation being due in part to a direct physico-chemical interaction with cholesterol in the membrane exofacial or outer leaflet [50].

The biochemical relation of cholesterol and Aβ is bidirectional. Several studies have demonstrated that Aβ affects the cellular cholesterol dynamics, such as cellular transport, distribution and binding, which in turn has a variety of effects on AD related pathologies, including the modulation of tau phosphorylation, synapse formation and the maintenance of its function, and the neurodegenerative process. On the other hand, cholesterol is implicated in APP processing and Aβ generation and in the amyloid cascade, leading to disruption of synaptic plasticity, promotion of tau phosphorylation, and eventual neurodegeneration [51,52]. *In vitro* studies indicate that the cellular cholesterol content modulates Aβ production and the enzymatic processing of APP [53–56]. Animal studies demonstrate that cholesterol modulates Aβ accumulation in the brain [57,58]. Several observational, clinical studies suggest that the prevalence and incidence of probable AD are lower in patients taking cholesterol-lowering drugs [59,60].

It has been suggested that the changes in neurochemistry of Aβ, tau, neuronal cytoskeleton, and oxidative stress reactions in the case of AD could represent physiological transitory mechanisms aiming to compensate impaired brain cholesterol dynamics and associated neurotransmission and synaptic plasticity failure [61].

Aβ and membrane-related toxicity. It has been suggested recently that pathological interactions of Aβ peptide with neuronal membranes might not only depend on the oligomerization state of the peptide, but also on the type and nature of the supramolecular Aβ — membrane assemblies inherited from Aβ's origin [62]. By using a combination of magic angle spinning nuclear magnetic resonance and circular dichroism spectroscopy, fundamental differences in the functional organization of supramolecular Aβ_{1-40} membrane assemblies for two different scenarios with potential implications in AD have been reported: (i) Aβ peptide can either be firmly anchored in a membrane upon proteolytic cleavage, thereby being prevented from being released and aggregated or (ii) it can have fundamentally adverse effects when bound to membrane surfaces by undergoing accelerated aggregation, which causes neuronal apoptotic cell death. Acidic lipids can prevent release of Aβ_{1-40} inserted in the membrane by stabilizing its hydrophobic transmembrane *C*-terminal part in an alpha-helical conformation. However, if Aβ_{1-40} is released as a soluble monomer, charged membranes act as two-dimensional aggregation-templates on which an increasing amount of charged lipids causes a dramatic accumulation of surface-associated Aβ_{1-40} peptide followed by accelerated aggregation into toxic structures [62].

In conclusion, Aβ can induce membrane-related toxicity by one or several of the following mechanisms (for a review, see [24]):

(i) Aβ influences the fluidity of the lipid bilayer through strong physicochemical interactions with the membrane [35,36].
(ii) Aβ is inserted into the membrane, thereby perturbing the structure of the plasma membrane and leading eventually to membrane fusion [63]. It has been demonstrated that insertion of Aβ in the membrane is controlled by the ratio of cholesterol to phospholipids.
(iii) oligomeric Aβ promotes the release of lipid such as cholesterol, phospholipids and monosialoganglioside from neuronal membrane, which may lead to the disruption of neuronal lipid homeostasis and the loss of neuronal function [64].
(iv) Aβ peptides can form ion channels in lipid bilayers, liposomes, neurons, oocytes and endothelial cells. These channels possess distinct physiological characteristics that would be consistent with their toxic properties. Aβ channels are heterogeneous in size, selectivity, blockade and gating. They are generally large, voltage-independent, and relatively poorly selective amongst physiological ions, admitting Ca^{2+}, Na^{+}, K^{+}, Cs^{+}, Li^{+} and possibly Cl^{-}. The Ca^{2+} influx via Aβ-channels destabilizes cellular Ca^{2+} homeostasis and induces neurotoxicity ([65,66] and for reviews, see [67,68]).

INTERACTION OF Aβ WITH MEMBRANE PROTEINS

Investigations of the interactions between Aβ and membrane proteins are usually motivated by an interest in a phenomenon relating to the dysfunction of a specific target protein or its involvement in AD.

A subset of membrane proteins binds Aβ, inducing various effects on neurons (Figure 4) and glial cells (Figure 5). The biochemical characteristics of these proteins are summarized in Table 1.

It has been demonstrated that the conversion of Aβ from a soluble to a fibrillar form markedly increases its binding to membrane proteins. The radioactive labelling of $A\beta_{1-39}$ has revealed that the binding of this peptide to cortical homogenates (containing both lipids and membrane-associated proteins) is correlated with the proportion of the aggregated peptide form in the solution [69].

Proteins that Bind Non-fibrillar Aβ

Insulin receptor. Binding assays have revealed that $A\beta_{1-40}$ and $A\beta_{1-42}$ compete with insulin for binding to the insulin receptor [70]. It is suggested that the binding of Aβ to the insulin receptor involves the $A\beta_{16-25}$ sequence, because it presents a recognition motif common to the 21–30 sequence of insulin, which is implicated in the binding of insulin with its receptor. This binding has been investigated with regard to the facts that (i) insulin and Aβ share a common sequence recognition motif, (ii) Aβ and insulin are substrates for the same

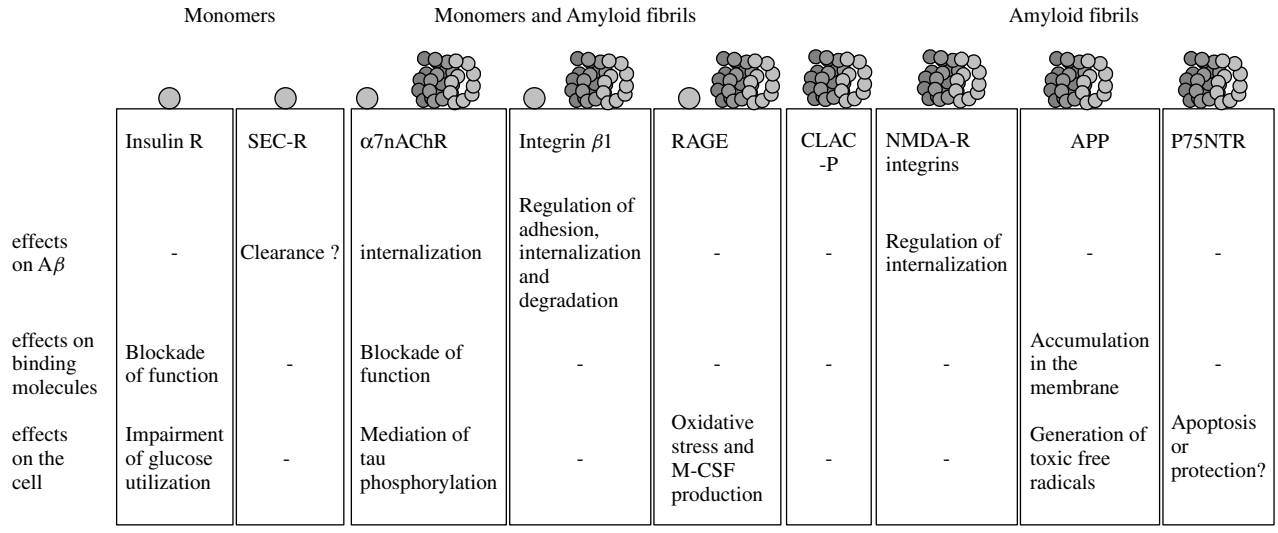

Figure 4 Interaction of β-amyloid with plasma membrane proteins of neurons.

Table 1 Cellular Expression, Biochemical Structure and Functions of Membrane Proteins Described as Aβ-binding Proteins

Protein	Expression	Biochemical structure	Functions	Reference
Insulin receptor	Neurons, glial cells, other cell types (liver)	Cell membrane protein composed of a tetramer of two α and two β subunits, which are derived from the cleavage of a single precursor glycoprotein of 1382 amino acids	The α chains contribute to the formation of the ligand-binding domain, while the β chains carry the kinase domain	[70,140]
SEC-R	Neurons, glial cells, other cell types	Transmembrane protein with a ligand-binding subunit of 84 kDa	Receptor of α1-antitrypsin–elastase complexes, mediating their endocytosis and intracellular degradation	[78]
α7nAChR	Cholinergic neurons	Integral membrane protein pentameric structure	Modulates Ca^{2+} homeostasis and acetylcholine release	[84,87,141]
Integrin β_1	Widespread in most tissues	Heterodimers composed of one α and one β subunit. Seventeen types of α and 8 β subunits have been described. All α and β subunit types (except β_4) are transmembrane glycoproteins	Involved in cell adhesion, motility, proliferation, apoptosis, induction of gene transcription and differentiation	[88–90]
RAGE	Ubiquitous	Type I transmembrane form and secreted form	Mediates the actions of advanced glycosylation end products	[99]
FPRL1	Inflammatory cells, other cell types	G-protein-coupled transmembrane receptor integral membrane protein of 351 amino acids, potentially glycosylated	Receptor of low affinity for N-formyl-methionyl peptides, which are powerful neutrophil chemotactic factors	[104]
NMDA-R	Neurons	Heterodimers of one ε subunit and one zeta subunit integral membrane proteins, may be glycosylated. Allosteric site for glycine which must be occupied	Functions of NMDA-R regulated by integrins involved in clathrin-mediated endocytosis	[92,142,143]
APP	Neurons	Type I transmembrane glycoprotein several isoforms (695, 714, 751 or 770 amino acids), which result from alternative modes of splicing	Physiological roles in synaptic action, brain development, and the responses to stress and injury	[111]
CLAC-P/collagen type XXV	Neurons	Type II transmembrane collagen-like protein 654-amino acid protein with an apparent molecular mass of 80 kDa, may be glycosylated	Cleaved by furin and secreted	[114]
P75NTR	Neurons	Type I transmembrane protein N- and O-glycosylated. Monomeric form and a trimeric form	Nonselective neurotrophin receptor belonging to the death receptor family. Can mediate the survival and death of neurons	[118]
SR-A, SR-BI	Glial cells and macrophages	Type I membrane proteins, with a large extracellular part, which mediates the binding and the degradation of acetylated low-density lipoproteins	Mediate the interactions of macrophages with many proteins, suggesting a function as adhesion protein	[127]
Scavenger receptor CD36	Glial cells, macrophages, others	Integral membrane glycoprotein of 471 amino acids localized in specialized membrane compartments known as lipid rafts	CD36 is an oxidized low-density lipoprotein receptor	[131]
CD47 (CD36, $\alpha_6\beta_1$-integrin)	Microglia cells	Integral membrane glycoprotein of 323 amino acids. It is a 50 kDa single-chain protein, composed of an extracellular immunoglobulin superfamily domain, five membrane-spanning sequences and a short cytoplasmic tail	Interacts functionally with both β_1 and β_3 integrins, and may serve to modulate integrin signalling functions and cellular adhesion. Interacts also physically with intracellular signalling complexes and integrates signals generated through ligand binding at the cell surface	[132,144]
HSP	Microglia cells, ubiquitous	Associated with the cell surface and the extracellular matrix of a wide range of cells	Essential cofactors in cell-matrix adhesion processes, in cell–cell recognition systems, and in receptor–growth factor interactions	[134,145]

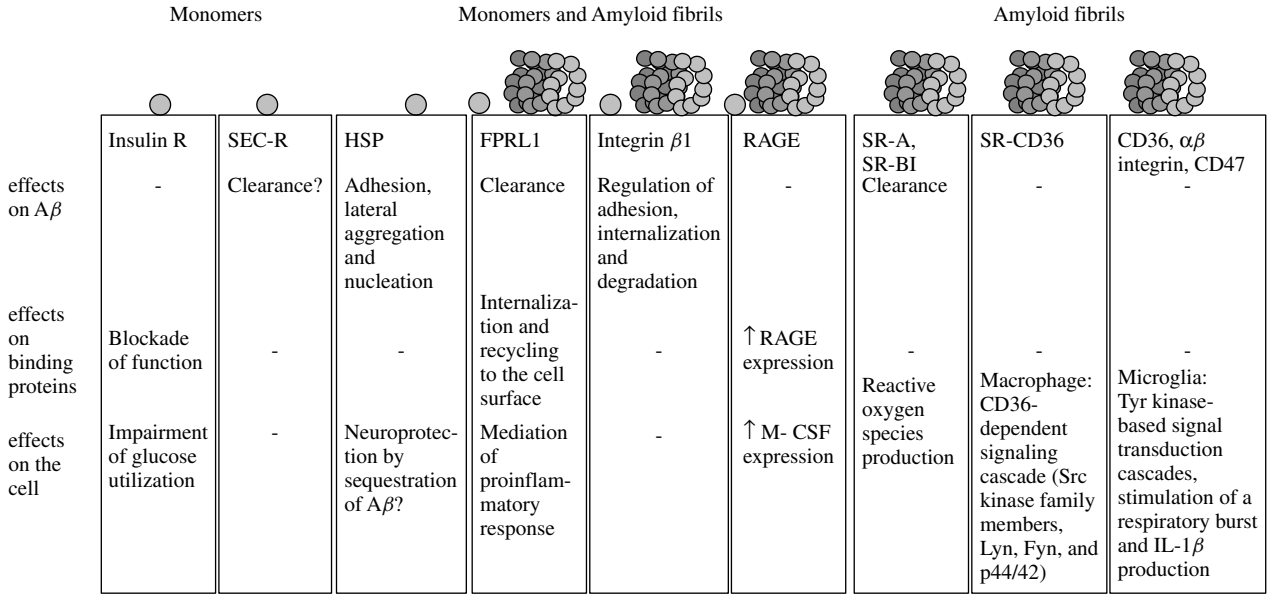

Figure 5 Interaction of β-amyloid with plasma membrane proteins of glial cells.

insulin-degrading enzyme, and (iii) an impaired glucose metabolism is a characteristic feature in AD [70]. It has also been reported that Aβ can interfere directly with insulin receptor signalling, inhibiting the autophosphorylation of insulin receptors [71].

This hypothesis supports the view that the soluble form of Aβ may also be toxic [72]. Increasing evidence exists that neuronal glucose metabolism and its control by the insulin signal transduction cascade are the main factors in memory formation and memory retrieval processes, such as adenosine triphosphate, acetylcholine or soluble APP metabolisms [73]. Any damage in neuronal glucose metabolism and its control may, therefore, cause disturbances in memory function, as is found for example in sporadic AD (for a review, see [74]).

Serpin complex receptor. Studies aimed at defining the minimal requirement for binding have found that the serpin complex receptor (SEC-R) could bind the FVFLM pentapeptide similar to the sequence of Aβ_{31-35} [75]. Competitive binding studies have shown that SEC-R mediates the endocytosis and degradation of soluble Aβ by recognizing the Aβ_{25-35} region in a sequence-specific manner [76]. Binding of SEC-R by various ligands can induce an increase of intracellular Ca^{2+}, however, an antagonist of this receptor scarcely inhibited the Ca^{2+} increase induced by Aβ, suggesting that SEC-R does not mediates this mechanism [77]. Moreover, the aggregated form of Aβ does not compete for binding to SEC-R. These data imply that SEC-R does not mediate the cytotoxic effect of fAβ, but could play a protective role by mediating the clearance and catabolism of soluble, monomeric Aβ [78].

Proteins that Bind both Fibrillar and Non-fibrillar Form of Aβ

Acetylcholine receptors. Various effects of Aβ on nicotinic acetylcholine receptors have been reported, suggesting that distinct mechanisms are involved in Aβ-induced cholinergic dysfunctions (for a review, see [68]).

The α7 nicotinic acetylcholine receptor (α7nAChR) is an integral membrane protein, which modulates Ca^{2+} homeostasis and acetylcholine release, two important parameters involved in cognitive and memory processes. α7nAChR is also involved in the known cytoprotective actions of nicotine [79]. It has been demonstrated that α7nAChR and Aβ_{1-42} are co-localized in neuritic plaques and neurons in AD, forming a stable complex as a result of a high-affinity interaction probably involving the 12–28 sequence of Aβ. The very high-affinity binding of Aβ_{1-42} to α7nAChR can be inhibited by α7nAChR ligands [80]. The interactions of monomeric or oligomeric forms of Aβ_{1-42} and Aβ_{1-40} with the α7nAChR result in different physiological responses as revealed by acetylcholine release and Ca^{2+} influx experiments [81].

While $A\beta_{1-42}$ effectively attenuates these α7nAChR-dependent responses to an extent that is apparently irreversible, $A\beta_{1-40}$ displays a lower inhibitory activity that can be restored upon washing with physiological buffers or treatment with α7nAChR antagonists [82]. It has been shown by voltage clamping on *Xenopus* oocytes expressing α7nAChR that the binding of nonaggregated $A\beta_{1-42}$ activates this receptor at picomolar concentrations, whereas at higher concentrations (nanomolar) a less effective receptor activation is observed, indicating receptor desensitization [83]. In another study on rat hippocampal neurons in culture, whole-cell patch-clamp recording demonstrated that nanomolar concentrations of $A\beta_{1-42}$ can block the function of α7nAChR specifically, reversibly and with high affinity. This blockade is noncompetitive and is exerted through the *N*-terminal extracellular portion of the receptor [84]. It has been suggested in AD that the interaction of Aβ peptides with α7nAChR may enhance toxicity by interfering with the cytoprotective actions of nicotine [85]. Further studies, including immunohistochemistry on consecutive sections and transfected neuroblastoma cells expressing high levels of the α7nAChR, suggest that the intraneuronal accumulation of $A\beta_{1-42}$ occurs predominantly in neurons expressing α7nAChR. Moreover, the internalization of $A\beta_{1-42}$ may be facilitated by its high-affinity binding to α7nAChR on the neuronal cell surface, followed by endocytosis of the resulting complex [86].

It has recently been reported that $A\beta_{1-42}$ elicits rapid and reversible tau protein phosphorylation, a hallmark of AD, in experimental systems enriched in α7nAChR. Western blotting analyses showed that the α7nAChR may mediate Aβ-induced tau protein phosphorylation via extracellular signal-regulated kinases and c-jun terminal kinases, as these mitogen-activated kinase cascade proteins were activated by $A\beta_{1-42}$, and this Aβ-induced tau phosphorylation is suppressed by their inhibitors [87].

It has been demonstrated that perfusion of low quantities of Aβ decreases the affinity of α4β2 nicotinic acetylcholine receptor for its ligand. This finding suggests that this subtype of receptor is also a target of Aβ, by direct binding or via an intracellular mechanism [68].

Integrins. It has been demonstrated that integrins can interact with Aβ [88,89]. From studies of the physiological roles of Aβ and APP, it has been established that several β_1 integrins mediate the cell adhesion of Aβ, and it has been proposed that $\alpha_5\beta_1$ is the integrin responsible for Aβ binding. The amino acid sequence RHD of Aβ, which is structurally close to the general integrin recognition sequence RGD, has been pinpointed as the integrin recognition site [89,90]. Via radioactive labelling of Aβ on CHO (Chinese hamster ovary) cells engineered to express $\alpha_5\beta_1$, it has been demonstrated that this integrin mediates the cell adhesion to nonfibrillar Aβ and also its internalization and degradation. Therefore, $\alpha_5\beta_1$ is able to decrease the formation of the insoluble fAβ matrix and protects against Aβ-induced apoptosis [91]. It should be noted that, in this study, cells expressing $\alpha_5\beta_1$ integrin did not exhibit any detectable adhesion to aggregated fAβ.

An integrin antagonist (GRGDSP peptide) has been reported to block the binding and uptake of Aβ in CHO cells [91], but it can also enhance Aβ uptake on cultured hippocampal slices, as demonstrated by immunocytochemistry [92]. Different cell types express different combinations of integrins [93] and to express their effect, integrins interact with different neighbouring transmembrane proteins. In addition, the adhesive connections that emerge with hippocampal maturation can serve to limit or block the entry of Aβ into neurons [92]. The enhancement of Aβ uptake by integrin antagonists suggests that integrins can regulate Aβ internalization by different mechanisms [92]. (1) A decrease in Aβ binding to integrins could increase the concentration of Aβ available for uptake by non-integrin mechanisms. Aβ bound to integrins can be proteolysed extracellularly. (2) Integrins connected to the extracellular matrix can suppress the processes that mediate Aβ internalization. (3) Integrins can also influence the trafficking and breakdown of internalized Aβ. Accordingly, other receptors may mediate cellular interactions with fAβ and be responsible for the cytotoxic effects of this form of Aβ.

AD is characterized by neuronal dystrophy and cell death in different areas of the brain (for a review, see [3]). Neuronal dystrophy and cell death induced by fAβ take place over different time courses and at different Aβ concentrations, suggesting that these two phenomena are mediated by separate molecular mechanisms. It has been proven that neuronal dystrophy can be induced by $fA\beta_{1-40}$ [94]. Other experiments have demonstrated that Aβ-induced dystrophy is mediated by the aberrant activation of focal adhesion proteins [95]. Given that focal adhesion sites are integrin-based structures that mediate cell-substrate adhesion, and the fact that

APP is colocalized with integrins in neurons, it has been suggested that APP may bring Aβ fibrils into physical contact with integrin receptors [95].

Complement receptor 3 (CR3) is an $\alpha_M\beta_{2-}$ integrin complex expressed on many monocyte, macrophage and neutrophil cell types in the immune system and in microglia, in the central nervous system [96]. It has been demonstrated (i) that CR3 is colocalized with factor H and agrin within the Aβ plaque; and (ii) that factor H binds agrin and fAβ. On the basis of these data, a model has been proposed wherein factor H binds to agrin in Aβ plaques, and then attracts or stabilizes infiltrating activated microglia via factor H binding to microglial CR3 [97].

Receptor for advanced glycosylation end products. It has been demonstrated that a scavenger receptor, the receptor for advanced glycosylation end products (RAGE), can bind Aβ and mediate its effects on neurons and microglia [98,99].

The binding of Aβ to the neuronal RAGE generates oxidative stress, which activates the transcription factor nuclear factor kappa B (NFKB), enhancing the expression of macrophage-colony stimulating factor (M-CSF). M-CSF released by neurons stimulates receptors on microglia cells, inducing an increased expression of ApoE and macrophage scavenger receptor and enhancing microglia cell proliferation and migration [98]. These data delineate an inflammatory pathway consistent with the pathological findings in AD. However, trypsin treatment alters the RAGE function, but not Aβ toxicity, and glycated albumin (a major ligand for RAGE) does not modify the Aβ response suggesting that other neural receptors for Aβ may mediate Aβ neurotoxicity [100].

An increased M-CSF expression has also been demonstrated after the direct addition of Aβ_{1-42} to microglia derived from AD brain. Treatment of microglia with anti-RAGE antibodies was found to block the stimulation of M-CSF secretion and to inhibit the chemotactic response of the microglia toward Aβ_{1-42}. Incubation of microglia with M-CSF and Aβ increased the expression of RAGE messenger ribonucleic acid. These microglial cells also expressed M-CSF receptor messenger ribonucleic acid. These data suggest a positive feedback loop in which Aβ-RAGE-mediated microglial activation enhances the expression of M-CSF and RAGE, possibly initiating an ascending spiral of cellular activation [101]. It has been revealed by immunohistochemistry that Aβ, advanced glycosylation end products and RAGE are colocalized in granules of astrocytes from AD brains. This finding indicates that glycated Aβ is taken up via RAGE and is degraded through the lysosomal pathway in astrocytes [102]. It should also be mentioned that a secreted form of RAGE also exists, termed hRAGEsec, which lacks the 19 amino acids of the membrane-spanning region and could be a prominent cell surface receptor interacting with Aβ [103].

Formyl peptide receptor-like 1. The G-protein-coupled transmembrane receptor FPRL1 (formyl peptide receptor-like-1) may serve as a receptor which mediates the proinflammatory responses elicited by Aβ_{1-42}. In the brain, FPRL1 has been found in a variety of cells, such as phagocytic leukocytes, lymphocytes, epithelial cells, microvascular cells and astrocytes [104].

Investigation of the capacity of Aβ_{1-42} for activating cells which are transfected to express FPRL1 or formyl peptide receptor (chemotaxis, calcium flux assay) showed that Aβ_{1-42} is a chemotactic antagonist for FPRL1, which is expressed at high levels by inflammatory cells infiltrating senile plaques in the brain tissues of AD patients. It should be noted that Aβ incubated at 37 °C displayed a reduced potency to induce cell migration, suggesting that fAβ is recognized by FPRL1 with lower efficacy [104]. Other works have demonstrated that interaction of Aβ with FRLP1 is clearly associated with cell activation and the release of proinflammatory and neurotoxic mediators [105].

Aβ_{1-42} associated with FPRL1 and the Aβ_{1-42}/FPRL1 complexes were rapidly internalized into the cytoplasmic compartment of mononuclear phagocytes, as demonstrated through the use of fluorescence confocal microscopy. Persistent exposure of the cells to Aβ_{1-42} over 24 h resulted in the retention of Aβ_{1-42}/FPRL1 complexes in the cytoplasmic compartment and the formation of Congo red-positive fibrils in the macrophages. These results suggest that besides mediating the proinflammatory activity of Aβ_{1-42}, FPRL1 is also involved in the internalization of Aβ_{1-42}, which culminates in the formation of fibrils only in the macrophages, inducing a cytopathic effect as shown by an increase in the proportion of apoptotic cells [106,107].

Although the fibrillar formation of the internalized Aβ could induce cell death, the uptake of Aβ by these cells may also serve as a maintenance of a dynamic balance between amyloid deposition and removal, a process that determines the amyloid burden in AD brain [108].

Proteins that Bind only the Fibrillar Form of Aβ

N-methyl-D-aspartate receptor and integrins. Integrins produce their effect on cell surface functions by interacting with neighbouring transmembrane proteins such as the N-methyl-D-aspartate receptor (NMDA-R). Direct Aβ–integrin interactions were discussed previously. Accordingly, any influence of NMDA-Rs on the integrin-regulated internalization of Aβ was studied [92]. The uptake of $A\beta_{1-42}$ by cultured hippocampal cells was assessed by immunohistochemistry in the presence or absence of the selective NMDA-R antagonist D-(-)-2-amino-5-phosphonovalerate. In the presence of the antagonist, the internalization of Aβ was completely blocked, as were two other characteristics of the early stages of AD, the upregulation of cathepsin D and the activation of microglia. It should be noted that uptake of Aβ, upregulation of cathepsin D, and the activation of microglia were enhanced by the administration of the integrin antagonist peptide GRGASP. Integrins and NMDA-Rs could therefore regulate the internalization of $A\beta_{1-42}$ cooperatively. It is interesting to consider that the effects obtained with integrins and NMDA-R manipulations are related, e.g. that a decreased binding of Aβ to integrins by antagonists enhances the effect of NMDA-R on Aβ sequestration [92]. These data are consistent with other results [109], which established that memantine, a noncompetitive NMDA-R antagonist, could protect against neuronal degeneration induced by Aβ.

Amyloid precursor protein. Aβ interacts with APP [110]. In AD, APP plays a role as the precursor of Aβ [111]. In cortical neurons, any involvement of APP in the mechanism of neuronal degeneration was investigated [110]. A co-precipitation assay was used to purify membrane proteins that bind to fAβ, and a subsequent western blotting assay demonstrated that Aβ interacts with the transmembrane form of APP and, to a much lesser extent, with the secreted forms of APP (fragments of ~600 amino acids derived from the extracellular amino-terminal domain) [110].

Recently, it has been demonstrated in primary cultures of neurons and astrocytes, using immunoblotting and electron microscopy, that APP binds a variety of fibrillar peptides derived from proteins associated with different diseases ($A\beta_{1-42}$, $A\beta_{25-35}$, prion $protein_{106-126}$, prion $protein_{178-193}$, and human amylin), but not the non-fibrillar form of these peptides [112]. This binding results in the accumulation of soluble APP on the cell surface and stabilization of membrane-bound holo-APP. The accumulated APP can increase the level of Cu(II) reduction via the APP copper binding domain, promoting the generation of toxic free radicals such as $OH^{\bullet}$ from Cu(I). This would induce lipid peroxidation and subsequent neuronal cell death [112].

It has been shown that binding of fAβ to the cell surface might occur in a protein complex containing APP [110]. It has been reported that the β-amyloid binding protein (BBP) may be a component of this complex. BBP is a membrane-associated glycoprotein, containing a G protein-coupling module. The BBP subtype bound to human Aβ *in vitro* with high affinity and specificity. Expression of BBP in cell culture induced caspase-dependent vulnerability to fAβ peptide toxicity [113].

Collagen-like Alzheimer amyloid plaque component precursor. It has been established that both the secreted form and the membrane-tethered form of collagen-like Alzheimer amyloid plaque component precursor/collagen XXV (CLAC-P/Col XXV) bind specifically to fAβ [114]. The binding of CLAC/Col XXV to fAβ is completely blocked in the presence of 0.5 M NaCl, implying an ionic interaction. When secreted, CLAC colocalizes with Aβ in amyloid deposits in the brain. The CLAC protein has the same chromatographic and immunological profile as AMY, a protein found to co-elute with Aβ in insoluble fractions from human AD brain and absent in brains from control subjects [115]. Further work is necessary for a better evaluation of the role of CLAC-P in AD, such as investigations of the distribution of CLAC-P in the brain and analysis of the effects of fAβ binding on the physiological function and the turnover of CLAC-P.

P75 neurotrophin receptor. The P75 neurotrophin receptor (P75NTR) is a nonselective neurotrophin receptor belonging to the death receptor family; it can be bound by nerve growth factor, brain-derived neurotrophin factor, neurotrophin-3 and neurotrophin-4. This receptor can mediate the survival and death of neurons. In the brain, this protein is expressed at the highest level by the cholinergic neurons of the basal nuclear complex, which are sensitive to Aβ neurotoxicity, and undergo degeneration in AD (for a review, see [68]). In contrast, the neurons of other cholinergic complexes in the brain (pedunculoponine and lateral tegmental nuclei) neither express P75NTR nor undergo degeneration in AD, suggesting that the vulnerability of basal nuclear neurons and

their projections may be related to their high-level expression of P75NTR [116].

The use of rat cortical neurons and a cell line engineered to express P75NTR has demonstrated that P75NTR binds specifically fAβ, and that this binding is followed by apoptosis [117,118]. The binding of Aβ to P75NTR activates NFKB in a time- and dose-dependent manner. Blockade of the interaction between Aβ and P75NTR with nerve growth factor or inhibition of NFKB activation by curcumin or NFKB SN50 attenuated or abolished Aβ-induced apoptotic cell death [119]. Other studies have shown that P75NTR may be present in a trimer form that binds Aβ to induce receptor activation, and that Aβ binds to both the P75NTR trimer and the P75NTR monomers [118]. In neuronal hybrid cells, it has been confirmed that P75NT mediates Aβ toxicity, and that the P75NTR-mediated Aβ neurotoxicity involves G_o, c-jun kinase, reduced nicotinamide adenine dinucleotide oxidase and caspases 9/3 [120].

However, it has been reported that, in human primary neurons in culture, P75NTR protects against extracellular Aβ-mediated apoptosis. This neuroprotection might occur through a P13K-dependent pathway. The reason for this difference may be explained by differential activation of a signal transduction pathway in primary neurons versus tumour cell lines, a cell-type or species-specific effect of Aβ, or a differential expression of the other neurotrophic receptors [121].

Scavenger receptor. Microglial cells, the mononuclear phagocytes of the brain, have been shown to express the scavenger receptors of classes A (SR-A) and BI (SR-BI), CD36, RAGE and low-density lipoprotein receptor-related protein (LRP).

The role of RAGE has been discussed above. LRP and its ligands (ApoE-containing lipoproteins, activated α2-macroglobulin complexes and APP) have all been genetically linked to AD and are colocalized in senile plaques (for a review, see [122]. LRP1 and LRP2 bind Aβ and exert a neuroprotective action on Aβ clearance, but only when Aβ is complexed with ApoE, ApoJ or α2-macroglobulin [123–125]. Therefore, the role of LRP will not be detailed further.

SR-A and SR-BI. SR-A and SR-BI present on glial cells bind to fibrillar $A\beta_{1-42}$ specifically, and appear to mediate the clearance of small fibrillar aggregates *in vitro.*

SR-A has been reported to mediate the adhesion of rodent microglia and human monocytes to Aβ fibril-coated surfaces leading to the secretion of reactive oxygen species (ROS) and cell immobilization [126]. CHO cells transfected with SR-A or SR-BI exhibit a significantly enhanced binding and uptake of $A\beta_{1-42}$ [127,128]. Binding to SR-A and SR-BI can activate inflammatory responses via ROS production that contributes to the pathology of AD [129]. However, the use of SR-ligands has shown that SR-A is not required for fAβ-induced microglial activation [130].

CD36. CD36, a class B scavenger receptor, has been described as a receptor for fAβ. Bowes human melanoma cells, which normally do not express CD36, gained the ability to bind specifically to surfaces coated with $fA\beta_{1-42}$ when transfected with a cDNA encoding human CD36, suggesting that CD36 is a receptor for fAβ [131]. Furthermore, two different monoclonal antibodies to CD36 caused an approximately 50% inhibition of the H_2O_2 production of microglia and human macrophages adhering to surfaces coated with fAβ, which suggests a role of CD36 in fAβ-induced H_2O_2 production by microglia, also implying that CD36 can mediate binding to fAβ [131]. It has been demonstrated that binding of fAβ to CD36 mediates activation of microglia to produce ROS, the proinflammatory cytokines interleukin (IL) -1β and tumor necrosis factor α, and a number of chemokines active on microglial cells. CD36 dependent chemokine secretion promotes the recruitment of additional activated microglia, which would amplify the local neurotoxic inflammatory response [22]. fAβ activates a CD36-dependent signalling cascade involving the Src kinase family members, the inflammatory mediators Lyn and Fyn, and the mitogen-activated protein kinase p44/42. [22]. It has been proposed that, similar to their role in the interaction of macrophages with oxidized low-density lipoprotein, SR-A and CD36, and perhaps RAGE, they play complementary roles in the interaction of microglia with fAβ [22,131].

Complex CD36, integrin and CD47. A multireceptor complex including the B-class scavenger receptor CD36, $\alpha_6\beta_1$–integrin and the integrin-associated protein CD47 has been described as mediating the binding of microglia to fAβ and the subsequent activation of intracellular signalling pathways leading to a proinflammatory response [132]. The integrins and CD36 have been discussed above.

The search for a multireceptor complex arose from the recognition that myeloid lineage cells

utilize multiple cell surface receptors to bind fibrillar proteins, and the assembly of ensembles of receptors is necessary for cellular activation. It has been established that antagonists of scavenger receptors (fucoidan), and more precisely CD36 (peptides), antagonists of integrin subunits α_6 and β_1 (antibodies) and antagonists of CD47 (peptides), are able to inhibit the adhesion of f$A\beta_{1-42}$, f$A\beta_{1-40}$ and f$A\beta_{25-35}$ to microglia and subsequent activation of the intracellular Tyr-kinase-based signal transduction cascades, leading to the stimulation of a respiratory burst and IL-1β production. These receptors do not interact with the nonfibrillar form of Aβ [132].

Aβ INTERACTIONS WITH GLYCOSAMINOGLYCANS

Heparan sulfate proteoglycans (HSPs) have been described as cell-surface binding sites for Aβ. HSPs are considered to be central elements in the pathology of AD as they play a role in Aβ plaque pathogenesis, Aβ binding, Aβ plaque formation, APP processing, Aβ fibril formation, neurofibrillary tangle formation, the ApoE-mediated lipoprotein metabolism, growth factor signalling, cytokine signalling, neurite outgrowth, cell adhesion and complement regulation (for a review, see [97]).

HSPs bind the HHQK site of APP [133]. Small peptides containing the HHQK sequence inhibit $A\beta_{1-42}$-microglia cell binding. This amino acid sequence corresponds to the 13–16 domain of Aβ, which binds to microglia cells. Binding tests have proven that the Aβ binding to microglia is sensitive to heparitinase cleavage and to competition with heparan sulfate, which suggests that plaque–microglia interactions (through the HHQK domain of Aβ) are mediated by membrane-associated heparan sulfate [134]. Studies involving the use of affinity chromatography have proven the binding between Aβ and HSP, and with a dermatan sulfate proteoglycan. Binding was also demonstrated by a chemically deglycosylated protein core preparation [135].

Other experiments, including the addition of competitive substances to the cell culture medium, cell-surface treatment, and the specific blockade of cellular synthesis pathways helped to identify the heparan sulfate moiety of a glycosyl-phosphatidylinositol-anchored protein likely to present glypican as a possible receptor for mediating Aβ neurotoxicity [136].

The interactions of glycosaminoglycan with $A\beta_{1-40}$ and $A\beta_{1-42}$ have been studied by means of circular dichroism spectroscopy, fluorescence spectroscopy and electron microscopy [137]. The presence of heparin, heparan sulfate, keratan sulfate or chondroitin sulfates has been demonstrated to accelerate the transition of monomeric Aβ peptides to the β-sheet. This is accompanied by the appearance of well-defined amyloid fibrils indicating an enhanced nucleation of $A\beta_{1-42}$. These findings add to the picture of the Aβ-glycoaminoglycan interactions, which include nonspecific adhesion to plaque, the lateral aggregation of preformed fibrils and Aβ nucleation in the earliest stage of fibril formation [137].

In conclusion, sulfated glycosaminoglycans (sGAG) strongly favour Aβ polymerization. Moreover, this binding has been found to decrease Aβ degradation, which is presumably catalysed by the insulin degrading enzyme. Thus, sGAG might enhance the polymerization of Aβ into fibrils. On the other hand, sequestration of extracellular Aβ aggregates by sGAG may prevent the interaction of Aβ with neuronal membrane (for a review, see [138]).

CONCLUSIONS

The binding of Aβ to the plasma membrane appears to be a critical step in the events leading to the development of AD. Indeed, the biochemical relation of membrane and Aβ is bidirectional.

It appears that Aβ binding to some membrane proteins may be protective for the cell, e.g. by mediation of Aβ adhesion, internalization and degradation (NMDA-R and integrins [92]; $\alpha_5\beta_1$ integrins [91]; SEC-R [78]. Perturbation of these functions may facilitate the development of AD. On the other hand, Aβ can induce membrane-related toxicity by perturbation of the membrane fluidity or membrane structure, release of lipids from the neuronal plasma membrane or formation of ion channels. Aβ binding to some proteins can damage the cell by mediation of tau protein phosphorylation (α7nAChR, [87]), generation of oxidative stress and stimulation of macrophages (RAGE ([98], SR-A and SR-BI, [129]; SR-CD36 [131], FRLP1 [104]), blockade of protein function (α7nAChR, [83]; insulin receptor, [70]), or induction of apoptosis via c-Jun pathway (P75NTR [118]).

Binding of Aβ to the membrane could also have consequence on Aβ itself. For example, non-specific adhesion of Aβ to HSP facilitates lateral aggregation

of preformed fibrils and Aβ nucleation at the earliest stage of fibril formation [137].

The variety of fAβ-binding proteins led to the suggestion that a multireceptor complex may be involved in this interaction, such as CD36, $\alpha_6\beta_1$-integrin and CD47 in the microglia [132], factor H, agrin and $\alpha_M\beta_2$-integrin in the microglia [97], NMDA-R and $\alpha_5\beta_1$-integrin in the neurons [92], or APP and integrins in the neurons [95]. The integrins seem to play a pivotal role in each of these complexes.

The binding of Aβ to membrane proteins could be specific in the sequence or conformation of Aβ (for example, α7nAChR binds to Aβ_{1-40} with a lower affinity than to Aβ_{1-42}), configuration of Aβ (monomeric or fibrillar), or the presence of modulatory factors (for example, Aβ_{1-40} is known to activate tachykinin receptors strongly only when it acts in synergy with glutamate [139]). Some of these molecules such as APP or sGAG could also bind a variety of fibrillar peptides involved in various neurodegenerative disorders [112], leading to the question of the existence of common mechanisms in case of these diseases.

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