# Pharmacology of the Intracellular Pathways Activated by Amyloid Beta Protein

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**Abstract:** Alzheimer's disease (AD) is a late-life cognitive disorder associated, among other things, to the presence of extracellular aggregates of fibrillar amyloid beta protein (Aβ). However, there is growing evidence that early stages of AD may be due to neuronal network dysfunction produced by the actions of soluble forms of Aβ. Therefore, the development of new therapeutic strategies to treat AD, at least during its first stages, may be focused on preventing or reversing, the deleterious effects that soluble Aβ exerts on neuronal circuit function. In order to do so, it is necessary to elucidate the pathophysiological processes involved in Aβ-induced neuronal network dysfunction and the molecular processes underlying such dysfunction. Over the last decades, there has been extensive research about the molecular mechanisms involved in the effects of Aβ as well as possible neuroprotective strategies against such effects. Here we are going to review some of the intracellular pathways triggered by Aβ, which involve membrane receptors such as nicotinic-R, NMDA-R, integrins, TNF-R1, RAGE, FPRL and p75NTR and their intracellular mediators such as GSK3, PKC, PI3K, Akt, FAK, MAPK family, Src family and cdk5. Several of these pathways may constitute therapeutic targets for the treatment of the Aβ-induced neuronal network dysfunction which is, at least in part, the basis for cognitive dysfunction in AD.

**Key Words:** Alzheimer's disease, Aβ-signaling pathways, neuronal network dysfunction, Aβ-related receptors and pharmacological targets.

## INTRODUCTION

Alzheimer's disease (AD), the most common of the late-life dementias, frequently begins after the age of 60 years and its prevalence rises exponentially with age, reaching more than 40% of people over 85 [1]. Symptomatically, AD is characterized by a progressive impairment in cognitive function [2-5] whereas histopathologically, AD is characterized by the presence of extracellular aggregates of fibrillar amyloid beta protein (Aβ) [4, 6] and intracellular aggregates of hyperphosporylated Tau-protein [7, 8]. Up to date, there is increasing evidence indicating that early soluble forms of Aβ, rather than late fibrillar conformations, might interfere with normal neuronal network function and consequently lead to the early deficits in learning and memory observed in AD patients [5, 9, 10] as well as in transgenic AD animal models, long before any neurodegeneration is observed [5, 11-15].

The Aβ is a 39-43 amino acid peptide cleavage product derived from the amyloid precursor protein (APP) [4, 16, 17], which is generated by the sequential processing of two proteases, β-secretase and γ-secretase, through the amyloidogenic pathway. Alternatively APP can be processed by α-secretase, which precludes the formation of Aβ in the nonamyloidogenic pathway [18].

Aβ-induced dysfunction seems to be associated to neuronal network alterations both at the physiological and biochemical levels, and involves a complex mixture of effects on neurons and glia [5, 19]. Altogether, the deleterious effects of Aβ on neuronal networks may affect cognitive-related processes such as long term potentiation (LTP) *in vivo* and *in vitro* [15, 20-27], neuronal network oscillations *in vivo* and *in vitro* [28-30] as well as neuronal codification *in vivo* [31]. These effects might represent the basis for the cognitive decline observed, at least, during the early stages of AD [15, 20-23, 25-29]. Accordingly with this line of evidence, we have recently shown that acute application of Aβ affects hippocampal network functioning from single cell to network level both *in vitro* and *in vivo* [30]. But what is the biochemical source of such network dysfunction?

Finding the biochemical events involved in Aβ-induced neuronal network dysfunction will provide with proper therapeutic targets to treat AD, at least during its initial phase. This is an important issue due to the fact that there are no therapeutic interventions available that halt or reverse AD and that the currently approved anti-AD therapies, including the cholinesterase inhibitors and the N-methyl-D-aspartic acid receptor (NMDA-R) antagonists (for review see [32-35]), just offer modest symptomatic relief [36]. We believe that new therapeutic targets might be revealed through the study of the putative Aβ membrane receptors and the intracellular pathways triggered by Aβ. Here we are going to review the intracellular pathways involved in the generation of Aβ-induced neuronal network dysfunction. We are including the receptors and the intracellular pathways altered by Aβ on all types of nerve cells, since it is well known that brain function is generated by the complex interaction of a neuroglial network and since it is very likely that Aβ-induced neuronal network dysfunction is the product of a complex altera-

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tion induced by Aβ in both neurons and all types of glial cells [5, 37, 38]. Finally, it is important to mention that we are going to review the receptors and the intracellular pathways known to be directly activated or modified by Aβ. In almost all the cases the reviewed data refers to the intracellular pathways activated by acute Aβ application, however we also include few data involving effects produced by long-lasting Aβ application, in such cases we indicated that the biochemical events were evoked by long-lasting Aβ application. The review of several neuroprotective intracellular pathways that might prevent the effects of Aβ, but that are not directly activated by such protein, has been previously done and are not going to be reviewed here (see [38-41]).

## Aβ-RELATED RECEPTORS AND ITS INTRACELLULAR PATHWAYS

As was previously described, Aβ is a peptide related to neurodegeneration and the progressive impairment of cognitive function in AD, therefore a great effort has been done to determine if such effects are mediated by putative Aβ receptors. The literature shows that Aβ can bind to several types of membrane receptors and can activate different signaling pathways through them [42, 43]. Such receptors include a) Ion channels like NMDA-R and nicotinic receptors (nAChR); b) G-protein-coupled receptors such as the formyl-peptide receptor-like-1 (FPRL1); c) Adhesion receptors like integrins; d) Cytokines receptors like p75 neurotrophin receptor (p75NTR) and tumor necrosis factor receptor 1 (TNF-R1); e) Tyrosine kinase receptors like insulin receptors (IR); and f) A variety of receptors that share their participation in the inmmune response, such as the receptor for advanced glycation end products (RAGE), scavenger receptor A (SR-A) and BI (SR-BI), as well as cluster of differentiation 36 (CD36), 14 (CD14) and 47 (CD47) [42, 43]. All those reeptors, and their interactions with Aβ, will be reviewed next.

### NMDA-R

One of the major targets for Aβ seems to be the glutamatergic NMDA-R, to which directly binds (Fig. **1**) [44]. There is overwhelming evidence that NMDA-R play a major role in Aβ-induced neurotoxicity and sinaptotoxicity [5, 45-49]. Accordingly, Aβ-induced increase of intracellular $Ca^{2+}$ results from the interaction of Aβ and NMDA-R (Fig. **1**) [50, 51] and Aβ-induced neurotoxicity is usually reverted by NMDA-R antagonists [49, 52]. A recent report indicates that those neurons that express NMDA-R with the NR1/NR2A subunit composition are more vulnerable to Aβ-induced neurotoxicity [53]. Furthermore a recent report has shown that Aβ-induced activation of NMDA receptors requires a tyrosin phosphorylation of the NR2B subunit [54].

As mentioned, Aβ-induced neuronal death involves the activation of NMDA-R. Accordingly, in MES 23.5 neuroblastoma cell line, Aβ-induced neuronal death is enhanced in $Mg^{2+}$ free media and inhibited in $Ca^{2+}$ free media, as well as by the application of 5-methyl-10,11-dihydro-5H-dibenzo [a,d]cyclohepten-5,10-imine (MK-801), an NMDA-R antagonist [55]. Aβ-induced, NMDA-mediated, neuronal death involves the increase of $Ca^{2+}$-dependent nitric oxide (NO) synthesis and the subsequent overproduction of guanosine cyclic monophosphate (GMPc) and the radical oxygen species (ROS) (Fig. **1**) [55]. Beyond the possible direct activation of NMDA-R by Aβ, a possible indirect activation of the same receptor seems to be achieved by the effect of Aβ on microglia. *In vitro* studies have shown that activation of microglia by Aβ produce the secretion of both tumor necrosis factor-α (TNFα) and glutamate, as part of the pro-inflammatory reaction [56-58]. Both TNFα and glutamate synergistically promote neuronal death trough the activation of TNF receptor 1 (TNFR1) and NMDA-R. This conclusion is based on the fact that memantine and 2-amino-phosphonovaleric acid (APV), both NMDA-R antagonists, as well as soluble TNFR1, protects neurons from Aβ-induced neuronal death [59]. Related to this finding, it has been observed that, at chronic level, cholinergic denervation produced by Aβ correlates with an increase of NO production, which is mediated by $Ca^{2+}$ influx *via* NMDA-R activation. Interestingly, chronic exposure to ifenprodil tartrate, which selectively binds to the NMDA-R2B subunit, prevented all the described effects [60, 61]. In contrast to the evidence just reviewed, a recent report has shown that prolonged exposure of organotypic hippocampal slices to Aβ dimers and trimers can induce a progressive loss of dendritic spines and a decrease in excitatory synapses. Such effects can be prevent with antibodies against Aβ or with an Aβ aggregation inhibitor called scyllo-inositol (AZD-103) [62]. This Aβ-induced spine loss seems to be produced by a reduction of $Ca^{2+}$ influx through NMDA-R, since a subsaturating concentration of 3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid (CPP), a NMDA antagonist, mimicked Aβ-induced effect [62]. It is important to mention that this finding contrast with published literature showing the Aβ activates NMDA-R and induce Ca2+ influx through them (Fig. **1**) [50, 51].

Aβ interaction with NMDA is not exclusively related to $Ca^{2+}$ influx and neurotoxicity (Fig. **1**), it can also induce the activation of several transduction pathways that may lead to changes in neuronal function before cell death (Fig. **1**) [5]. Electrophysiological experiments have shown that Aβ increases NMDA-R dependent, currents [63] or NMDA-dependent responses [64] and that this potentiation of NMDA-currents is involved in the increase of LTP produced by Aβ [65]. Aβ interaction with NMDA-R, triggers the activation of different protein kinases such as Src-like kinases (including Fyn), Ras, the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) (Fig. **1**). In granule neurons Aβ-induced, NMDA-R-mediated, nuclear factor κB ($NF_{\kappa}B$) activation is inhibited by 4-Amino-5-(4-chlorophe-nyl)-7-(*t*-butyl) pyrazolo[3,4-d]pyrimidine (PP2), manumycin A, PD98059 and LY294002, inhibitors of the mentioned proteins, respectively (Fig. **1**) [66]. The activation of MAPK by Aβ, through NMDA-R activation, has also been observed in hippocampal neurons [67]. Furthermore Aβ induces Akt phosphorylation through the activation of both NMDA and α7nChRs; effect blocked by ifenprodil and methyllycaconitine (MLA), both antagonists of the mentioned receptors, respectively (Fig. **1**) [54]. Altogether the evidence reviewed show that blocking the potentiation of NMDA-dependent mechanisms produced by Aβ represents an attractive therapeutic target against AD. In fact it might constitute the cellular basis for the beneficial clinical effects observed with NMDA-R antagonists, being the more successful example that of memantine [49, 52, 68, 69].

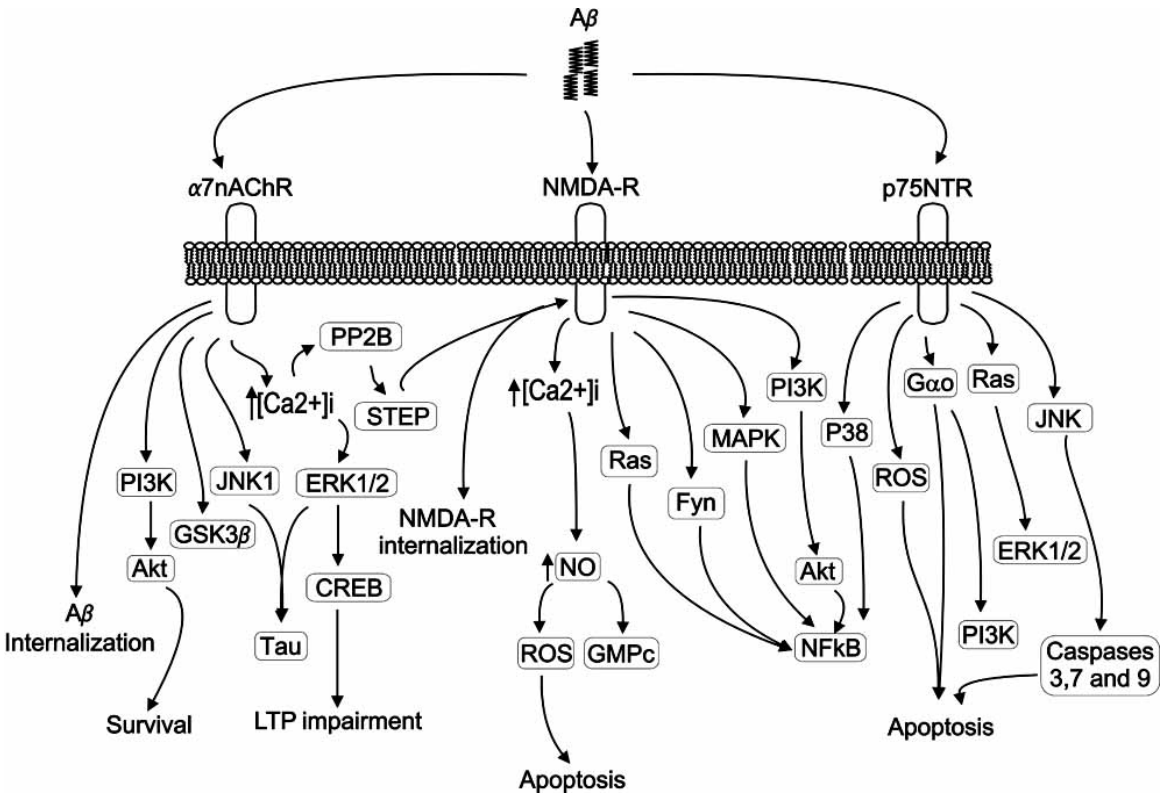


**Fig. (1). Main receptors and intracellular pathways activated by Aβ in neurons.** Without ignoring other neuronal receptors, Aβ can bind and activate nicotinic-, NMDA- and p75NT receptors in neurons. Activation of such receptors induces both ion movements and biochemical cascades. A major component of the response to Aβ in neurons is a raise in intracellular calcium through the nicotinic and the NMDA receptors. It is important to mention that such receptors activate several biochemical pathways as well. Both receptors, along with p75NTR, share the activation of members of the MAPK-family as a key players of their triggered intracellular pathways. Abbreviations: **Aβ**: amyloid beta protein; **CREB**: cAMP response element binding; **ERK1/2**: extracellular signal-regulated kinase 1 and 2; **GMPc**: guanosine cyclic monophosphate; **GSK3β**: glycogen synthase kinase 3β; **JNK1**: c-Jun N-terminal kinase 1; **MAPK**: the mitogen-activated protein kinase; **NFκB**: nuclear factor κB; **NMDA-R**: N-methyl-D-aspartic acid receptor; **NO**: nitric oxide; **p75NTR**: p75 neurotrophin receptor; **PI3K**: phosphoinositide 3-kinase; **PP2B**: protein phosphatase 2B; **ROS**: reactive oxygen species; **STEP**: striatal-enriched phosphatase; **α7nAChR**: α7 nicotinic receptors.

## Nicotinic Receptors

The nicotinic receptors (nAChR) are ligand-gated ion channels [70-73], consisting of five subunits with eight different α (α2-α9) subunits and three different β (β2-β4) components [74]. Of these nAChR, α7 and α4β2 are the most abundant combinations in the brain [75]. The α7nAChR is highly expressed in the hippocampus and the cortex. Those brain areas, which are related to memory and cognition, are highly innervated by the basal forebrain cholinergic neurons, and are the most disturbed brain areas in AD [71, 73, 76-84].

Although there are some reports showing that Aβ acts independently of nicotine receptors [4, 85], a great pool of evidence has proven that Aβ can bind nicotine receptors and activate intracellular pathways through them (Fig. **1**): immunohistochemical studies have shown that Aβ and α7nAChR colocalized on neurons surrounding neuritic plaques in hippocampal and cortical tissues from AD brains [86, 87]. Both Aβ and α7nAChR co-immunoprecipitate when antibodies against either Aβ or α7nAChR are used [86, 87]. Furthermore, binding assays have shown that Aβ bind with high affinity to α7nAChR (Fig. **1**) [86, 87]. Whether or not Aβ acts as an agonist or as an antagonist for α7nAChR remains controversial and will be discussed later [88-90]. In relation to intracellular signalling, Aβ interaction with α7nAChR activates PI3K, extracellular signal-regulated kinase (ERK) and Akt (Fig. **1**) [88, 91-93]. Binding of Aβ to α7nAChR can activate ERK2, in a $Ca^{2+}$-dependent manner (Fig. **1**). This effect is blocked by the α7nAChR antagonists MLA and α-bungarotoxin (BTX) [88]. Related to this finding, it has been observed that a transgenic AD mouse model (Tg2576), shows an age-dependent increase both in α7nAChR expression as well as in ERK2 activation in the hippocampus and the cortex [88]. A similar effect has been observed using organotypic hippocampal slices incubated chronically with Aβ [88]. Chronic exposure to Aβ also induces changes in the

expression of nAChR. For instance, when PC12 cells are exposed chronically to Aβ, a down regulation of the mRNA codifying for α3, α7 and β2 nAChRs is observed [94]. In constrast, when Aβ is applied to neuroblastoma cell line SK-N-MC, that overexpress α7nAChR, a rapid binding, internalization and intracellular accumulation of Aβ is observed [95]. Incubation with the α7nAChR antagonist BTX, as well as with the endocytosis inhibitor phenylarsine oxide, prevents such internalization [88, 95]. Accordingly, the intracellular accumulation of Aβ observed in AD brain, colocalize with the presence of α7nAChR [86, 95].

Aβ interaction with α7nAChRs may eventually lead to Tau phosphorylation (Fig. **1**). In SK-N-MC cells expressing α7nAChR, as well as in cortical and hippocampal neurons, Aβ interaction with α7nAChR lead to the activation of ERK and c-Jun N-terminal kinase 1 (JNK1) and the subsequent phosphorylation of Tau (Fig. **1**) [96]. Such Aβ-induced Tau phosphorylation was suppressed with the α7nAChR antagonists BXT and MLA, as well as with the specific ERK inhibitors 5-iodotubercidin and roscovitine, and the JNK1 inhibitor SP600125 [96]. In differentiated PC12 cells, Aβ interaction with α7nAChR increases phosphorylation of Tau through the activation of glycogen synthase kinase 3β (GSK3β), such effect is blocked by the GSK3β inhibitor CHIR98023 (Fig. **1**). Surprisingly the effect was blocked by both an agonist (A-582941) and antagonists (MLA and BTX) of α7nAChR [97]. Based on this findings, authors suggested that blockade of Aβ-induced Tau phosphorylation by both an agonists and antagonists of α7nAChR, may be result of a net inhibition of α7nAChR either by the desensitization of the receptor with agonists or its inhibition with antagonists [97]. Aβ interaction with α7nAChR may also affect the function of NMDA-R. Snyder *et al.* have reported that Aβ can induce a α7nAChR-dependent reduction of NMDA-mediated responses. Such effect involves the activation of protein phosphatase 2B (PP2B) and tyrosine phosphatase striatal-enriched phosphatase (STEP) (Fig. **1**), since Aβ-induced α7nAChR-mediated reduction of NMDA responses is blocked by the α7nAChR inhibitors BTX and MLA, the PP2B inhibitor cyclosporine and a dominant-negative STEP protein [98].

As mentioned before, whether or not Aβ acts as an agonist or as an antagonist for α7nAChR remains controversial [88-90]. Regarding the agonistic action of Aβ on α7nAChR it has been reported a direct activation of recombinant rat α7nAChR by Aβ in *Xenopus* oocytes [99]. Same activation has been observed in native rat α7nAChR in synaptosomal preparations isolated from the hippocampus, the striatum and the cortex [100]. Accordingly, Aβ potentiates nicotine-induced $Ca^{2+}$ influx in rat basal forebrain neurons [101]. Furthermore, as mentioned, Aβ application to hippocampal slices activates, *via* α7nAChRs, ERK2 [88]. Finally, in primary neuronal cultures, blockade of α7nAChR with MLA, protects against Aβ-induced neurotoxicity [102].

Despite the evidence suggesting that Aβ may activate α7nAChR, there are reports suggesting otherwise. For instance, binding of Aβ to α7nAChR blocks native α7nAChR currents in hippocampal neurons [89, 103]. Same effect is observed in α7nAChR currents expressed in *Xenopus* oocytes [104-106] or in SH-EP1 human epithelial cells [107]. Similarly, Aβ application can impair LTP *in vivo* and *in vitro* by blocking α7nAChR activity [84, 108]. It has also been reported that α7nAChR activation either with nicotine and the specific agonist 3-(2,4)-dimethoxybenzylidene (DMXB) provide protection against Aβ-induced neurotoxicity [109, 110]. The neuroprotective effect of nicotine can be block by the nAChR antagonist hexamethonium and mecamylamine as well as the selective α7nAChR antagonist BTX [91, 109]. Furthermore, it has been reported that Aβ-induced cell death in SK-N-MC cell line, can be prevented either by nicotine or epibatidine, a potent α7nAChR agonist [86]. The neuroprotective effect of nicotine against Aβ-induced neurotoxicity can also be blocked by the PI3K inhibitors LY294002 and wortmannin as well as a Src-family inhibitor PP2, suggesting that these kinases are involve in the neuroprotective actions of nicotine [91, 93]. It has been proposed that, at least in the neuronal cell line PC12, nicotine competes with Aβ for the binding to α7nAChR and therefore prevents the Aβ-induction of caspase 3 and apoptosis [92]. This effect appears to be mediated by α7nAChR, because the protection is blocked by BTX and is mimicked by the α7nAChR agonist TC-1698 [92, 111, 112]. Interestingly, treatment with nicotine for ten days in the APPsw mice model reduced insoluble amyloid by 80% in the brain cortex of 9 month-old mice [113]. This effect is mediated, at least in part, by the α7nAChR as shown by using MLA [113]. Overall, despite the controversy regarding the agonistic or antagonistic actions of Aβ on α7nAChR, the evidence reviewed, clearly point toward α7nAChR as a very likely candidate for pharmacological manipulation in order to overcome Aβ-induced effects.

The evidence just reviewed support the notion that nicotinic receptors may constitute a promising target to treat AD. It is well know that smokers have less accumulation of Aβ [114] and a reduced risk to develop AD [115, 116]. Preliminar clinical studies have shown that transdermal application of nicotine improves memory and attention in AD patients [117, 118]. Similar improvements have been achieved through the administration of the nicotinic receptor agonist ABT-418 [119]. Furthermore, in AD transgenic models, it has been found that nicotine administration reduces Aβ accumulation [120] and improves the memory deficit observed in these animals [121]. Interestingly, it has been shown that immunization against α7 receptors improves the memory deficit observed in an AD animal model [122].

**p75NTR**

p75 neurotrophin receptor (p75NTR) is a transmembrane protein with a structure similar to the tumor necrosis factor receptor and CD40 [123]. Aβ can bind p75NTR (Kd = 23 nM) with a lower affinity than its natural ligand nerve growth factor (NGF) (Kd = 4-7 nM) in NIH 3T3 cells as well as rat cortical neurons (Fig. **1**) [124]. Aβ-p75NTR complex can contain either a sole p75NTR receptor (80 kDa) or a receptor complex of 230 kDa, proposed to be a trimer of p75NTR [123, 125]. A variety of different-length Aβ peptides interact with and activate p75NTR signaling (Fig. **1**); including aggregated Aβ 1–40 [123-125], soluble oligomeric and aggregated Aβ 1–42 [126-130] and oligomeric and aggregated Aβ 25–35 [123, 126, 131]. Binding of Aβ to p75NTR leads to cell death trough the interaction of Aβ with

the receptor's amino-terminal domain and the activation of a neurotoxic function of the receptor localized in its carboxyl-terminal domain [132] The specificity of this interaction is revealed by the fact that Aβ induces cell death in NIH 3T3 cells sobreexpressing p75NTR but has no effect on non-transfected cells [124]. Similar data was obtained using human neural crest-derived melanocytes [124]. These findings are confirmed by *in vivo* experiments showing that Aβ-induced neurodegeneration of basal forebrain cholinergic neurons is not observed in p75NTR-deficient mice [133]. Interestingly, basal forebrain cholinergic neurons have the highest levels of p75NTR in the brain and are one of the most affected neurons in AD [134]. Aβ binding to p75NTR triggers activation of the downstream signalling molecules such as JNK, $G_{i/o}$-proteins, NFκB and PI3K (Fig. **1**) [135]. The induction of cell death upon interaction of p75NTR with Aβ is mediated by the activation of caspases-8 and -3 and the production of ROS intermediates (Fig. **1**). Benzyloxycarbonyl-Val-Ala-Asp (OMe) fluoromethylketone (Z-VAD-FMK), a non-selective caspases inhibitor, and Z-IETD-FMK, a specific caspase 8 inhibitor, prevented such cell death [132]. As mentioned Aβ-induced p75NTR-mediated cell death, involves the activation of JNK and p38, as well as the mitogen-activated protein kinases MKK3, 4 and 6 and p53 activity (Fig. **1**) [126, 131, 132]. The activation of these proteins was found to require the death domain region of p75NTR [131, 132]. On F11-neuron hybrid cells, transfected with p75NTR, Aβ-induced p75NTR-mediated cell death, was mediated by $G_o$ (Fig. **1**). This was demonstrated by using the $G_{i/o}$ inhibitor *pertussis* toxin (PTX) [126]. In this case, JNK and caspases 3,7 and 9 are also involved in Aβ-induced p75NTR-mediated cell death (Fig. **1**), since the inhibitor of caspases 3/7 Ac-DEVD-CHO (DEVD), the inhibitor of caspase 9 Ac-LEHD-CHO (LEHD) and the JNK inhibitor SP600125, prevented cell death [126]. On human neuroblastoma cell line, the transcriptional factor NFkB is also activated during cell death promoted by Aβ (Fig. **1**) [123]. By blocking the interaction Aβ-p75NTR with NGF or the inhibition of NFkB activation by curcumin or NFkB SN50, respectively, Aβ-induced cell death was prevented [123]. Low concentrations of Aβ can activate Ras and ERK1/2 *via* p75NFR, in MDCK and RN22 cells as well as in cerebellar neurons (Fig. **1**) [129]. Interestingly, using a neuroblastoma cell line devoid of neurotrophin receptors and engineered to express either a full-length or a death domain (DD)-truncated form of p75NTR, Constatntini *et al.*, 2005 demonstrated that Aβ activates p38 and JNK and induces NFkB translocation through its carboxyl-terminal domain [131]. In a recent report is has been shown that blocking binding of Aβ to p75NTR, with an antagonist peptide (sequence CATDIKGAEC), produced a reduction in Aβ-induced neurotoxicity in NIH-3T3 cells and cortical neurons [136], as well as the neuroinflammatory response induced by Aβ in B57BL/6 mice [137]. Altogether, the evidence shows that p75NTR and its associated intracellular pathways, constitute very interesting candidates for the development of pharmacological strategies against Aβ neuronal network disruption.

**Integrin Signal Pathway**

Integrins are members of a superfamily of membrane glycoproteins that are well expressed in all cell types [138]. Such glycoproteins form heterodimers composed of α and β subunits that act as receptors for extracellular matrix proteins and counterreceptors on adjacent cells [138]. Integrin-mediated cell to cell interactions are necessary for cell survival, since loss of this function can cause apoptosis [139]. Furthermore, in the central nervous system, integrins are widely expressed in synapses and dendritic spines and can regulate synaptic transmission and plasticity [27, 138, 140-142]. For instance, integrins regulate the memory-related plastic mechanism called long-term potentiation (LTP) [139]. Integrins contain the Arg-Gly-Asp attachment site that allows their interactions with other proteins during cell adhesion process [143]. Interestingly for this review, it is known that integrins bind Aβ in an analog domain composed of the aminoacid sequence Arg-His-Asp-Ser (Fig. **2**) [144, 145]. Therefore, integrins and the intracellular pathways that can be evoked upon their activation have been related to AD (Fig. **2**).

Integrins co-localize with senile plaques and dystrophic neurites in AD patients, as well as in transgenic animal models of this disease [146-149]. Several are the consequences of Aβ binding to integrins (Fig. **1**); for instance, binding of Aβ to the integrin heterodimer α1β1, activate the MAPKK-ERK2 pathway and induces neurite degeneration and cell death in hippocampal neurons (Fig. **2**) [150], such effects were blocked by the general integrin inhibitor echistatin, as well as by antibodies against both α1 and β1 integrins [150]. When Aβ bind to α1 and β1 integrins, produce their internalization, and secondarily lead to apoptosis in SH-SY5Y cells [151]. In the same report, it was shown that treatment with integrin-binding proteins, such as fibronectin, laminin and collagen, protected against Aβ-induced apoptosis, and treatment with antibodies against both α1 and β1 integrins enhanced Aβ-induced neurotoxicity [151]. The later finding, was explained by suggesting that Aβ binding to integrins may disrupt their normal interaction with the extracellular matrix, which then triggers apoptosis, at least in SH-SY5Y cells. Another study, using the same cell line, showed that Aβ binds to α1 integrin and activates focal adhesion kinase (FAK) and ERK1/2 (possibly through a Fyn-dependent mechanism), inducing the reactivation of the cell cycle and ultimately cell death (Fig. **2**) [152]. The involvement of Fyn in this pathway was suggested by the inhibition of both processes with the Fyn inhibitor PP2, whereas the participation of FAK was revealed by its knock-down with an specific siRNA [152]. Other reports, using the SH-SY5Y cell line along with B103 cell and cortical neurons, have shown that Aβ increased the phosphorylation levels of FAK (Fig. **2**) [149, 153, 154]. It is important to mention that FAK is a tyrosine kinase [139, 155], closely related to Fyn kinase [156-159]. FAK and Fyn, which are overexpressed in AD brains [160, 161], participate along with PI3K, in Aβ-induced tyro-sin phosphorylation of microtubule-associated protein 2c (MAP2c) and TAU [154] (see Fig. **2**). We have recently shown that Aβ-induced hippocampal network dysfunction is precluded in Fyn-knockout mice suggesting that Fyn kinase play an important role in Aβ-induced pathology [30].

The disruption of normal integrin function by Aβ may lead neurons to the reactivation of cell cycle and ultimately death [152]. This might explain why there is a reexpresion in

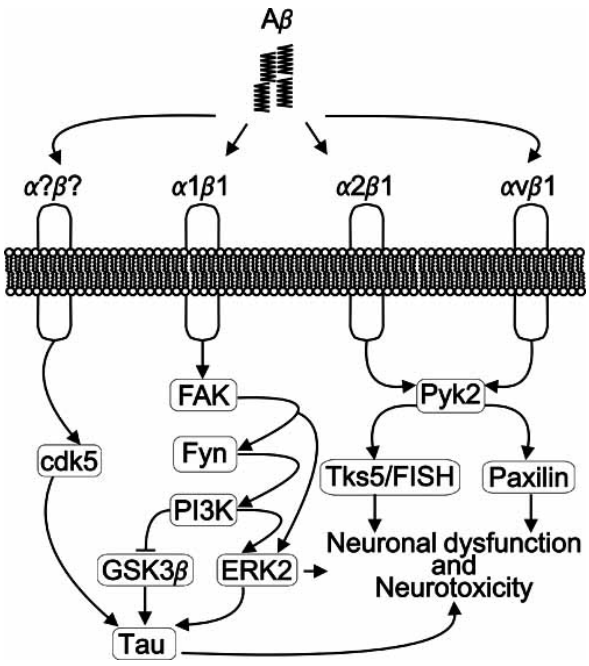


**Fig. (2). Aβ activates integrin-mediated pathways**. Aβ can bind and activate different types of integrins, including α1β1, α2β1 and αvβ1. Such activation induces several intracellular pathways that include as key players Pyk2, as a convergence kinase, and tyrosine kinases such as FAK and Fyn. Abbreviations: **Aβ**: amyloid beta protein; **cdk5**: cyclin-dependent kinase 5; **ERK**: extracellular signal-regulated kinase; **FAK**: focal adhesion kinase; **GSK3β**: glycogen synthase kinase 3 β; **PI3K**: phosphoinositide 3-kinase; **Pyk2**: proline-rich tyrosine kinase 2; **Tks/FISH**: adapter protein.

the brain of AD patients of proteins related with the cell cycle like cell division cycle 2 (cdc2), cyclin B1, cyclin-dependent kinase 4 (cdk4), cyclin D, p16 and cyclin E, [162-166], as well as in the brain of AD transgenic mice [167]. As known, most normal neurons do not express cell cycle-related proteins, due to the fact that they are arrested in Go, thus Aβ-induced reactivation of neuronal cell cycle destabilize their neuronal function and lead them to dead [152].

An alternative pathway activated by the interaction between Aβ and αvβ1 integrins, is the activation of proline-rich tyrosine kinase 2 (Pyk2) (Fig. **2**) [149, 168-170]. Such activation of Pyk2 then activates the adaptors proteins Tks5/FISH or Paxillin, which are involved in neuronal dysfunction and neurotoxicity [149, 168-170]. Interestingly, endogenous ligands of integrins, such as fibronectin and collagen, prevent the neurotoxic effects just described [168]. Finally, a recent report has shown that the reduction of LTP induced by soluble Aβ is blocked by antibodies against αv integrin both *in vivo* and *in vitro* [27]. Overall, the information reviewed shows that integrins are a major target of Aβ. The intracellular pathways triggered by this interaction may lead to both neuronal dysfunction and death, and therefore this molecular system constitutes a potential therapeutic target against Aβ-induced neuronal network dysfunction and possibly against AD.

**Microglial Receptors (SR-A, FPRL1 and CD36/a6b1/CD47)**

A hallmark in the AD disease is a potent inflammation response promoted by activated microglial cells [171]. It has been reported that microglial cells surround senile plaques [172, 173] and that Aβ promotes cytokines production by those cells [174-176]. Furthermore microglial cells are not just activated by Aβ but phagocytes it [177-179]. Overall, these results indicate that microglial cells represent a key factor for understanding AD and for providing with therapeutic target against the disease. Several are the putative receptors that may be involved in Aβ-induced activation of microglial cells (Fig. **3**), including receptor for advanced glycation end products (RAGE), tumor necrosis factor receptor (TNF-R) as well as several microglial receptors such as scavenger receptor A (SR-A), formyl peptide receptor-like 1 (FPRL1) and a complex called CD36/α6β1/CD47 (Fig. **3**). We will review the interaction of Aβ with these four receptors next.

It is well known that senile plaques are surrounded by microglial cells that express the SR-A (Fig. **3**) [180-182]. SR-A was the first receptor shown to participate in binding and internalization of Aβ by microglial cells (Fig. **3**) [183, 184]. Subsequently, it has been reported that microglia from SR-A knockout mice bind Aβ less efficiently [185, 186]. Using human monocytes, N9 microglia cell line and primary rat microglial cells, it was found that Aβ binds to SR-A [183]. Upon binding to SR-A, Aβ inhibits cell migration (chemotaxis) and also promotes ROS production in those cells [183]. Also it has been reported that microglial cells internalize Aβ in a SR-A-dependent manner [184]. Similarly, the type BI SR receptor (SR-BI) also binds and internalize Aβ and induce ROS production in microglial cultures (Fig. **3**) [186].

The FPRL1, a Gi protein-coupled receptor involved in immune response [187, 188], is highly expressed by inflammatory cells infiltrating senile plaques in brain tissues from AD patients [189, 190]. Aβ binds and activates human FPRL1 (Fig. **3**) as well as its mouse counterpart FPR2, which activates microglial cells, promoting chemotaxis [190, 191]. Such effect can be blocked by desensitizing FPRL1 with its agonist fMLF [191]. When FPRL1 is sobreexpresed in HEK293 cells, Aβ activation of this receptor induces calcium influx and chemotaxis [190, 191]. Aβ can also be internalized upon binding to FPRL1, such internalization is involved in the intracellular aggregation of Aβ into microglia [187, 192]. Recently it has been shown that the FPRL1-mediated Aβ internalization is a phospholipase D (PLD)-dependent processes (Fig. **3**), which can be observed either in microglia or astrocites [193]. Such process can be reverted using the FPRL1 antagonist WRW4, as well as PTX [194].

The cluster of differentiation 14 (CD14) is the lipopolysaccharide (LPS) receptor [195], which is localized in microglial cells and seem to be another putative receptor for Aβ (Fig. **3**). For instance, coimmunoprecipitation of Aβ with CD14 was confirmed with binding assays, which show that Aβ binds CD14 with high affinity (Kd = 1 nM) [196]. Moreover, flow cytometry, confocal microscopy and two-photon fluorescence lifetime imaging (FLIM), combined

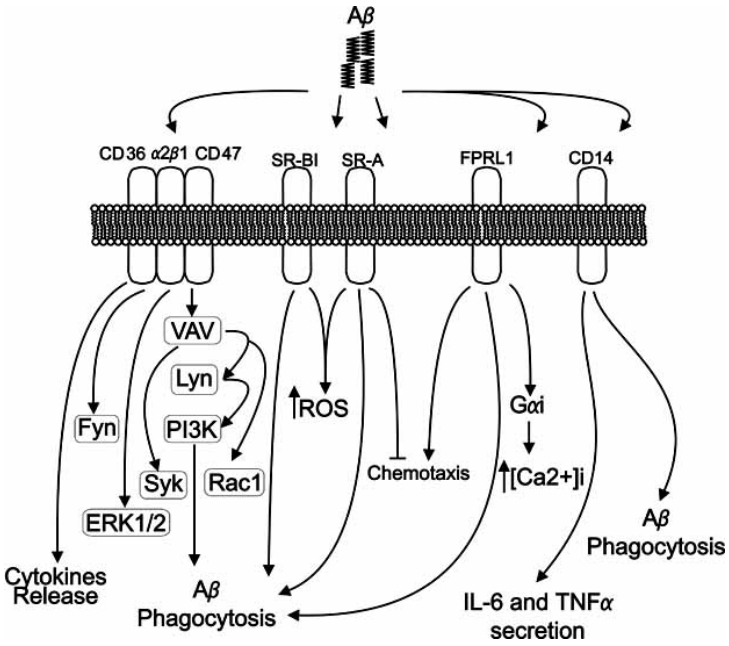


**Fig. (3). Main receptors and intracellular pathways activated by Aβ in microglia.** Most of the pro-inflammatory response induced by Aβ, involves microglial activation. This event is triggered by binding of Aβ to several types of receptors including scavenger receptors and "cluster of differentiation" (CD) receptors. In all cases, Aβ activation of such receptors leads to phagocytosis and/or cytokines release. It is important to mention that tyrosine kinases play a major role in the transduction of the receptor complex form by CD36 and 47 associated to integrin α2β1. Abbreviations: **Aβ**: amyloid beta protein; **CD14**: cluster of differentiation 14; **CD36**: cluster of differentiation 36; **CD47**: cluster of differentiation 47; **ERK1/2**: extracellular signal-regulated kinase 1 and 2; **FPRL1**: formyl peptide receptor-like 1; **IL-6**: interleukin 6; **PI3K**: phosphoinositide 3-kinase; **ROS**: reactive oxygen species. **SR-A**: scavenger receptor A; **SR-BI**: BI SR receptor; **TNFα**: tumor necrosis factor α.

with fluorescence resonance energy transfer (FRET), confirmed a direct interaction between Aβ and CD14 in CHO cells transfected with human CD14 receptor [197]. Interestingly, the Aβ-induced cytokine secretion (IL-6 or TNF-α) is not observed in microglial cells obtained from CD14 knockout mice [196]. As mentioned for the other microglial receptors, binding of Aβ to CD14 induces its internalization; which is dramatically reduced in microglial cells obtained from CD14 knockout mice [197].

At the microglial cell membrane, Aβ also interacts with a receptor complex composed of the B class scavenger receptor (CD36), α6β1-integrin and CD47, an integrin-associated protein (Fig. **3**) [198-200]. Aβ activation of this receptor complex induces tyrosine phosphorylation of several proteins; it also induces activation of Fyn kinase, ERK and eventually induces cytokine release (Fig. **3**) [198]. Inhibition of such receptor complex, with the scavenger receptor antagonist fucoidan, the CD47 inhibitor 4N1K, as well as with inhibitory peptides for CD36 and α6β1-integrin, reverted the effects just described [198]. Aβ interaction with this receptor complex also induces Aβ internalization in the immortalized murine microglia cell line BV-2 and primary microglia cultures [199]. Accordingly, application of some antagonists for several members of such receptor complex reduced Aβ internalization [199]. Such Aβ internalization seems to be mediated by the activation of Syk kinase (a member of Src-family tyrosin kinases) as well as by PI3K (Fig. **3**), since the application of the specific Syk inhibitor picetanol, the Src inhibitor PP2 and the PI3K inhibitor LY294002, blocked Aβ internalization [199]. A recent report has suggested that tyrosine kinase Vav is involved in the signaling pathway triggered by Aβ-induced activation of the receptor complex in human THP-1 monocytes [200]. This suggestion is based on the fact that Aβ-induced activation of the receptor complex in human THP-1 monocytes produces the activation of Lyn and Syk kinases in a Vav-dependent manner [200-202].

## RAGE

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin superfamily, composed of three extracellular Ig-like domains ($V_d$, $C_{1d}$, $C_{2d}$), a single transmembrane domain, and a short cytoplasmic tail [203, 204]. Interestingly for this review, RAGE is overexpressed in the brain of AD patients [205, 206] and constitutes a membrane binding site for Aβ (Kd = 50-100 nM) at neurons, microglial cells, as well as endothelial cells [205-209]. In those cells, Aβ-induced RAGE activation induces cell death [205, 210]. Accordingly, an antibody against RAGE prevents Aβ-induced cell death on SHSY-5Y cells sobreexpressing RAGE and rat cortical neurons stimulated with Aβ [203]. The receptor domains implicated in the neurotoxic effect were the $V_d$ for Aβ oligomeric forms and $C_{1d}$ for Aβ fibrillar

forms [203]. Regarding intracellular signaling, interaction of Aβ with RAGE, in SH-SY5Y cells, induces ERK1/2 and Akt phosphorylation through MAPK/ERK kinase 1 (MEK1) and PI3K respectively, since the MEK1 inhibitor PD98059, and the PI3K-inhibitor LY294002, abolished such activation [211]. Aβ interaction with RAGE also induces activation of IkBa and the NFkB translocation inhibitor SN50 [211]. However the activation of the two pathways just described seems not to be involved in Aβ-induced RAGE-mediated neurotoxicity. In contrast the JNK-inhibitor I and SB203580, a p38 inhibitor, reduced Aβ-induced RAGE-mediated neurotoxicity [211].

Aβ-induced RAGE activation in neuroblastoma cells increase the levels of macrophage colony-stimulating factor (M-CSF) and vascular cell adhesion molecule-1 (VCAM-1) through the activation of NFkB [212]. Interestingly M-CSF as well as VCAM-1 expression is increased in the brain of AD patients [212, 213] as well as the brain of AD mouse models [214]. Interestingly, M-CSF can activated microglia cells and enhance Aβ induced interleukin-1, interleukin-6 and NO production by such cells [215]. Microglial cells isolated from AD patients can release M-CSF upon Aβ activation of RAGE, since such release can be inhibited with antibodies anti-RAGE [206]. M-CSF is able to induce expression of RAGE which creates a positive loop that could favors the inflammatory process in AD [206].

A transgenic AD mouse model which overexpresses murine amyloid precursor protein (mAPP) and RAGE, displays functional abnormalities in spatial learning and memory, accompanied by promoting synaptic dysfunction and LTP reduction, as well as a progressive density decrease of cholinergic fibers and synapses, long before the same changes are expressed in mAPP transgenic mice [216]. An increase of NFkB traslocation, microgliosis and astrocitocis surrounding senile plaques, phosphorilated forms of cAMP response element binding (CREB), p38, ERK1/2, and calcium/calmodulin-dependent protein kinase II (CAMKII), was detected in the mAPP/RAGE mouse [216]. In contrast a transgenic mouse overexpressing mAPP along with a dominant-negative RAGE, shows a reduction in the alterations in spatial learning and memory, well as a decrease in neuropathologic changes, compared with the mAPP transgenic mice [216].

Despite many evidence that RAGE could mediate Aβ-induced neurodegeneration, in a report using PC12 cells, B12 cells or rat primary cortical neurons, it was shown that neurotoxicity by Aβ was not affected when RAGE was inactivated with trypsin [217].

### TNF-R1

Tumor necrosis factor (TNF, cachexin or cachectin and formally known as tumor necrosis factor-α, TNFα) is a cytokine involved in inflammation. Both TNFα and its receptor (TNF-R1) are increase in brain AD patients [218-222]. AD patients carrying the TNFα -308 A/G polymorphism and the apolipoproteinE (APOE) 4 allele had a lower mean age of AD onset [223]. AD brain microglia produce 1.5 times more TNFα than age with matched controls [224]. Aβ binds and activates TNF-R1 high affinity ($K_d$ = 0.42 nM). Aβ-induced activation of TNF-R1 promotes neuronal death by inducing the activation of NFkB and by altering the expression of the apoptotic protease-activating factor (Apaf-1) [220]. Such Aβ-induced TNF-R1-mediated apoptosis, along with the intracellular mechanisms just mentioned, is absent in a TNF-R1 knock out mice [220]. Recently it has been reported that the spatial learning alteration and the reduction of nerve terminals, observed in a mouse model of AD, are dependent on TNF-R1 [225]. Furthermore, it has been shown that the Aβ-induced inhibition of hippocampus LTP occurs as a consequence of release of endogenous TNFα and the subsequence activation of TNF-R1 mediated by Aβ oligomers [27]. Accordingly, Aβ-induced inhibition of hippocampus LTP is not observed in a mouse knock out for TNF-R1 [226]. Interestingly a prospective pilot study of 15 AD patients given a TNFα antagonist, etanercept, for 6 months showed significant improvement in 3 cognitive tests instead of the decline seen for untreated patients [227]. Furthermore, deletion of TNFR1 in APP23 transgenic mice prevents learning and memory deficits [228].

### Insulin Receptor

Aβ can also competitively bind and coimmunoprecipitate with insulin receptor (IR; Kd 8-25 mM); inhibiting receptor autophosphorylation and therefore blocking its signaling pathway [229-231]. Aβ also blocks IR-induced activation of ERK, CaMKII and Akt and these effects might be related to Aβ-induced inhibition of LTP, since the the Aβ-induced reduction in the activation of ERK, CaMKII and Akt is mimicked by the the IR antagonist AG1024 and Aβ-induced inhibition of LTP can partially be reverted by insulin [230]. Aβ can also induce the redistribution of IR, since Aβ application to hippocampal cultures produces a rapid and substantial loss of IR at dendrites surface, whereas produces an increased receptor immunoreactivity in the cell body [229]. Concomitantly with receptor redistribution, Aβ increases IR-mediated phosphorylation of Akt at serine473. The later is a molecular event related to neurodegeneration and insulin resistance [229].

## INTRACELLULAR PATHWAYS EVOKED BY AB WITH NOT IDENTIFIED MEMBRANE RECEPTOR ("ORPHAN" INTRACELLULAR PATHWAYS)

So far, we have reviewed several putative Aβ receptors and the intracellular pathways associated to them, however a careful review of the literature, shows a great amount of reports indicating that Aβ modulates several elements of different intracellular pathways, however the membrane receptor involved in such modulation remains undetermined [232-235]. However, due to the fact that several of those enzymes seem to be strongly related to the Aβ-induced effect and may constitute promising therapeutic targets against Aβ-induced effects, we want to mention some of them.

As already mentioned, several kinases known to phosphorylate Tau protein are activated by Aβ on neurons, including GSK3β and Cyclin-dependent kinase 5 (cdk5) [232-235]. Aβ also induce the activation of MAPKs in hippocampal and cortical neurons, as well as PC12 and SH-SY5Y human neuroblastoma cells, producing neurotoxicity [67, 236-238]. On THP-1 monocytic cell line, Aβ can activate ERK1/2 kinases [201]. Pretreatment with PP1 (the Src-family tyrosin kinase inhibitor) and piceatannol (a Syk kinase inhibitor) inhibited such ERK activation. Furthermore the calcium

ATPase inhibitors 2,5-ditert-butylhydroquinone (DTBHQ) and thapsigargin, the ryanodine receptor inhibitor dantrolene, as well as the calcium chelator 1,2-bis(o-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid (BAPTA), also decrease such Aβ-induced ERK activation suggesting that Lyn, Syk and intracellular store-mediated calcium rising are activated upon Aβ application to these cells [201]. The protein kinase C (PKC) inhibitor Go6976 (specific for calcium dependent PKC isoforms) also prevents Aβ-induced ERK activation. Same effect is achieved inhibiting Pyk2 and Lyn with the broad Src-like inhibitor PP1 [201]. A Pyk2 target called paxillin is also activated by Aβ in THP-1 monocites; such activation is blocked by the PKC inhibitor Go6976, the Src-like inhibitor PP1 and the calcium ATPase inhibitor DTBHQ [201].

It has been reported that Aβ induces the expression, in a PKC-dependent manner, of cyclooxygenase 2 (COX-2) which subsequent increases prostaglandin E2 release in primary midbrain astrocytes, such effect of Aβ can be blocked by the PKC inhibitor GF109203X [239]. Related to this finding, it has also being reported that Aβ can induce cyclooxygenase 1 activation and prostaglandin D2 production [240].

Intracerebroventricular injection of Aβ induces an inflammatory response in response the hippocampal CA1 area, characterized by astrocytes infiltration and the overexpression of interleukin-1b, caspase 3 and the pro-apoptotic protein FasL, as well as the activation of p38 MAPK [241]. In contrast, Aβ injection reduces the expression of several surviving-related proteins such as ERK1/2 and Akt/PKB [241]. Sodium ferulate (SF), which is extracted from *Scrophularia frutescens*, blocks the Aβ-induced increase in the the apoptotic pathway (p38MAPK, Caspase 3 and FasL) and the decrease of the survival pathway (ERK1/2 and Akt/PKB) [242]. Using the same experimental paradigm, intracerebroventricular injection of Aβ activates MKK3/MKK6, p38 MAPK and promotes an increase in IL-1b levels, while reduces activation of MAPKAPK-2 and its downstream target Hsp27 [243]. SF and the p38MAPK inhibitor SB203580 reverted such Aβ-induced effects [243].

Aβ application to retinal pericytes results in arachidonic acid (AA) production, such effect is reduced by applying the MEK inhibitor PD98059, the p38 MAPK inhibitor SB203580 and the PKC inhibitor GF109203X [176]. Same inhibitors also prevented Aβ-induced phophorylation and overexpression of phospholipase A2 [176].

As already mentioned, GSK3β is a major player in Aβ-induced neurotoxicity. For instance, the Aβ-induced neurotoxicity observed in primary cultures of embryonic rat hippocampal neurons is reduced when the culture is pretreated with a GSK3β antisense oligonucleotide [232]. Furthermore, Aβ-induced GSK3β-mediated neurotoxicity and Tau phosphorilation, seem to involve the inhibition of PI3K by Aβ [244]. In this experiment PI3K activity was determined by phosphatidylinositol (3,4,5)-trisphosphate (PIP3) production, and a decrease in PIP3 levels was observed upon Aβ application [244]. Finally, inhibiting GSK3β either with lithium or with the GSK3β inhibitor VIII prevents Aβ-induced Tau phosphorylation and neuronal death [234, 240]. These evidences are in agreement with clinical observations in AD patients. First of all, there is increased GSK3β activity in the frontal cortex in AD patients, as evidenced by immunoblotting for GSK3β phosphorylated at Tyr216 [245]. Furthermore, GSK3β expression is up-regulated in the hippocampus of AD patients [246] and in post-synaptosomal supernatants derived from AD brain [247]. GSK3β expression is also up-regulated in circulating peripheral lymphocytes in both AD and in mild cognitive impairment patients [248]. It has also been reported that a polymorphism in the GSK3β promoter as a risk factor for late onset AD [249]. Furthermore it has been observed that GSK3β co-localize with dystrophic neurites and neurofibrillar tangles [233, 247, 250, 251] and that active GSK3β is observed in neurons with pre-tangle changes [252].

Calcium/calmodulin regulated phosphatase or calcineurin, seem to be involved in Aβ-induced effects. For instance, Aβ-induced reduction of late-phase LTP in the hippocampal dentate gyrus involves Aβ-induced calcineurin activation [253]. Furthermore Aβ-induced neurotoxicity also involved the activation of calcineurin in cortical neuron primary cultures [254]. As known, calcineurin dephosphorylates and activates BAD, a proapoptotic member of Bcl-2 family, which triggers cytochrome c release and caspase 3 activation [255, 256]. Blocking calcineurin activity with FK506 or cyclosporine prevents neurotoxicity [253-256]. Interestingly in a transgenic mouse AD model, calcineurin activity is elevated and, on top of that, Aβ induces a further activation of calcineurin activity which then dephosphorylates and activates CREB, promoting cell death [257].

Finally Aβ-induced effects also seem to be dependent on the activation of a protein kinase called Fyn, a Src family tyrosine kinese member, which is widely expressed on the nervous system [157-159] and is increased in the brain of AD patients [160, 161]. Interestingly the described Aβ-induced LTP disruption and neurotoxicity is not observed in Fyn KO mice [21]. Furthermore the synaptotoxicity and cognitive impairments in a AD mouse model of AD seem to be mediated by Fyn [258]. As already mentioned, we have recently shown that Aβ-induced hippocampal network dysfunction is precluded in Fyn-knockout mice suggesting that Fyn kinase play an important role in Aβ-induced pathology [30].

## CONCLUDING REMARKS

The evidence reviewed show that Aβ interacts with a wide variety of membrane receptors and this interaction produces a complex response, involving several cell types, that eventually lead to neuronal network dysfunction, which then may be responsible for the early cognitive deficits observed in AD patients. The review of these receptors, along with the intracellular pathways associated with them, provide with promising therapeutic targets against Aβ-induced brain dysfunction and cognitive decline. However, it is important to identify which of these molecules, when pharmacologically activated or inhibited in order to overcome Aβ-induced effects, are associated with less side effects. It is important to take into account that the receptors and the intracellular pathways mentioned in this review are involved in several neuronal, and non-neuronal processes, which are important for normal brain function and that its pharmacological altera-

tion may be more harmful that the Aβ-induced effect. Thus the challenge for the coming years is to carefully dissect the Aβ-mediated molecular mechanisms to identify those therapeutic targets that may inhibit the Aβ-mediated neuronal network dysfunction without affecting normal brain function.

**ABBREVIATIONS**

| | | |
|---|---|---|
| AA | = | Arachidonic acid |
| AD | = | Alzheimer's disease |
| Apaf-1 | = | Apoptotic protease-activating factor |
| APOE | = | apolipoproteine |
| APP | = | Amyloid precursor protein |
| APV | = | 2-amino-phosphonovaleric acid |
| AZD-103 | = | Scyllo-inositol |
| Aβ | = | Amyloid beta protein |
| BAPTA | = | 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid |
| BTX | = | α-bungarotoxin |
| CAMKII | = | Calcium/calmodulin-dependent protein kinase II |
| CD14 | = | Cluster of differentiation 14 |
| CD36 | = | Cluster of differentiation 36 |
| CD47 | = | Cluster of differentiation 47 |
| cdc2 | = | Cell division cycle 2, also referred to as cyclin-dependent kinase 1 |
| cdk4 | = | Cyclin-dependent kinase 4 |
| cdk5 | = | Cyclin-dependent kinase 5 |
| COX-2 | = | Cyclooxygenase 2 |
| CPP | = | 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid |
| CREB | = | cAMP response element binding |
| DEVD | = | Ac-DEVD-CHO |
| DMXB | = | 3-(2,4)-dimethoxybenzylidene |
| DTBHQ | = | 2,5-ditert-butylhydroquinone |
| ERK | = | Extracellular signal-regulated kinase |
| FAK | = | Focal adhesion kinase |
| FLIM | = | Fluorescence lifetime imaging |
| FPRL1 | = | Formyl peptide receptor-like 1 |
| FRET | = | Fluorescence resonance energy transfer |
| GMPc | = | Guanosine cyclic monophosphate |
| GSK3β | = | Glycogen synthase kinase 3β |
| IR | = | Insulin receptor |
| JNK1 | = | c-Jun N-terminal kinase 1 |
| LEHD | = | Ac-LEHD-CHO |
| LPS | = | Lipopolysaccharide |
| LTP | = | Long term potentiation |
| MAP2c | = | Microtubule-associated protein 2c |
| MAPK | = | The mitogen-activated protein kinase |
| mAPP | = | Murine amyloid precursor protein |
| M-CSF | = | Macrophage colony-stimulating factor |
| MEK1 | = | MAPK/ERK kinase 1 |
| MK-801 | = | 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine |
| MLA | = | Methyllycaconitine |
| NFκB | = | Nuclear factor κB |
| NGF | = | Nerve growth factor |
| NMDA-R | = | N-methyl-D-aspartic acid receptor |
| NO | = | Nitric oxide |
| p75NTR | = | p75 neurotrophin receptor |
| PI3K | = | Phosphoinositide 3-kinase |
| PIP3 | = | Phosphatidylinositol (3,4,5)-trisphosphate |
| PKC | = | Protein kinase C |
| PLD | = | Phospholipase D |
| PP2 | = | 4-Amino-5-(4-chlorophenyl)-7-(*t*-butyl)pyrazolo[3,4-d]pyrimidine |
| PP2B | = | Protein phosphatase 2B |
| PTX | = | Pertussis toxin |
| Pyk2 | = | Proline-rich tyrosine kinase 2 |
| RAGE | = | Receptor for advanced glycation end products |
| ROS | = | Reactive oxygen species |
| SF | = | Sodium ferulate |
| siRNA | = | Small interfering RNA |
| SR-A | = | Scavenger receptor A |
| SR-BI | = | BI SR receptor |
| STEP | = | Striatal-enriched phosphatase |
| TNFR1 | = | TNF receptor 1 |
| TNFα | = | Tumor necrosis factor-α |
| VCAM-1 | = | Vascular cell adhesion molecule-1 |
| Z-VAD-FMK | = | Benzyloxycarbonyl-Val-Ala-Asp (OMe) fluoromethylketone |
| α7nChRs | = | α7 nicotinic receptors |

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