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Review

ADDLs and the signaling web that leads to Alzheimer's disease

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ABSTRACT

Today, it is widely accepted that ADDLs, soluble oligomeric assemblies of the amyloid β peptide, play a prominent role in triggering the cognitive deficits and neurodegeneration that constitute Alzheimer's disease (AD). Within the past decade, the longstanding emphasis on fibrillar deposits and neuronal death has given way to a new paradigm involving ADDL-triggered aberrant synaptic signaling and consequent memory malfunction and neurodegeneration. As with any paradigm shift in biology, not all molecular details have been elucidated, and not all AD scientists are fully subscribed. Nevertheless, the ADDL paradigm affords a promising framework for ongoing AD research and for development of the first therapeutics endowed with the dual capabilities of immediate symptom reversal and long-term disease modification. In this review we provide a brief account of the discovery of ADDLs, followed by a summary of key results that address questions concerning ADDL structure and assembly, biological activity and therapeutic possibilities.

1. The discovery of ADDLs

From the earliest descriptions of Alzheimer's disease (Alzheimer et al., 1991), amyloid plaques have been a central focus of discussions surrounding Alzheimer's disease etiology, but more than seven decades passed before the first molecular clue emerged – the 1984 discovery that the amyloid β peptide (Aβ) was the major protein constituent of neuritic plaques (Glenner and Wong, 1984). This led to discovery of the amyloid precursor protein (APP) gene in 1987 (Kang et al., 1987), and to the demonstration that fibrillar Aβ derived from synthetic peptide could be toxic to cultured neurons (Yankner et al., 1989). By 1990, publications on amyloid and AD numbered more than 500, and in a 1991 review (Selkoe, 1991), Selkoe wrote about "a slowly evolving cascade in which excessive deposition of Aβ plays an early and critical role". The following year, Hardy and Higgins proposed the "amyloid cascade hypothesis" and its central tenet that Aβ deposition and fibril-induced neuronal death caused AD (Hardy and Higgins, 1992). This hypothesis garnered support quickly, based on studies demonstrating that elevated production of profibrillar Aβ1–42 was the common consequence of many familial AD mutations found in *different* genes (APP, PS1 and PS2) [reviewed in (St George-Hyslop, 2000)]. Subsequent reports that Aβ only became neurotoxic when assembled into fibrils (Lorenzo and Yankner, 1994; Pike et al., 1993) reinforced the notion of central involvement of fibrillar Aβ.

Although appealing in many respects, the "amyloid cascade hypothesis" failed to reconcile a large body of clinical and pathology observations suggesting that AD cognitive deficits did not coincide with amyloid deposits. Indeed, careful analysis of plaque number and location showed little or no correlation with nerve cell loss and cognitive impairment in a number of studies (Hibbard and McKeel, 1997; McLean et al., 1999; Terry et al., 1991), and analysis of total amyloid load revealed little correlation with disease severity (Giannakopoulos et al., 2003). Transgenic mice were engineered to overproduce human Aβ, specifically to validate the amyloid cascade hypothesis, but instead, many Tg mice exhibited behavioral deficits long before the appearance of Aβ deposits or plaque pathology. These deficits coincided much more closely with synaptic loss (Hsia et al., 1999; Kawarabayashi et al., 2001; Mucke et al., 2000), a process not linked to plaques or Aβ deposition.

The first experiments to shed some light on this apparent plaque/fibril conundrum emerged in a 1995 publication, which proposed that soluble complexes of Aβ rather than Aβ fibrils were the molecular pathogens in AD (Oda et al., 1995). These soluble complexes formed when Aβ1–42 was mixed with small quantities of clusterin (apoJ), which resulted in a substantial suppression of fibril assembly and a surprising *increase* in neurotoxicity. These complexes were not isolated or characterized fully. However, the

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authors posited that the "soluble aggregated Aβ complexes could be formed at locations distant from plaques and could thereby cause neurotoxicity independent of plaques."

Follow-up studies by Lambert et al. (Krafft et al., 1998; Lambert et al., 1998) led directly to the biophysical and biological characterization of amyloid β-derived diffusible ligands (ADDLs), described as the *neurotoxic subset of soluble, non-fibrillar Aβ oligomers*. Atomic force microscopy and gel analysis revealed oligomeric structures estimated to contain ca. 3–24 peptide monomers, with neurotoxicity manifested through compromised neuronal ability to reduce the cell-permeant dye MTT, and by rapid disruption of long term potentiation (LTP) in organotypic hippocampal slices and anesthetized rats. The acronym "ADDLs" was selected to emphasize the soluble, non-fibrillar, and ligand-like nature of these Aβ assemblies, and the term ADDLs was intended to be more precise than the popular phrases "soluble Aβ" or "Aβ oligomers", which also include inactive assemblies.

The acceptance of ADDLs as the key molecular pathogens in AD continues to grow, as the number of supporting studies increases; (Rowan et al., 2007; Walsh et al., 2002, 2005); reviewed in (Catalano et al., 2006; Cerpa et al., 2008; El-Agnaf et al., 2000; Ferreira et al., 2007; Kirkitadze et al., 2002; Klein, 2000; Klein et al., 2001; Look et al., 2007; Marcello et al., 2008; Selkoe, 2008; Standridge, 2006; Viola et al., 2008; Walsh and Selkoe, 2007). The current view connecting ADDLs with AD is shown schematically in Fig. 1. This ADDL hypothesis resolves the plaque/fibril paradox inherent in the classical amyloid cascade theory by recognizing that the immediate AD-relevant consequence of elevated Aβ1–42 is increased ADDL formation, *not increased deposition*. Furthermore, functional deficits occur directly as a result of ADDL-triggered aberrant synaptic signaling, rather than from neuronal death instigated by plaques and fibrils. The ADDL hypothesis provides a simple explanation for the earliest subtle deficits, triggered by very low ADDL concentrations, and it also accounts for more severe late-stage deficits and accumulated biochemical and structural damage (e.g. tau phosphorylation and neurofibrillary tangles) caused by persistent downstream signaling that occurs over many years.

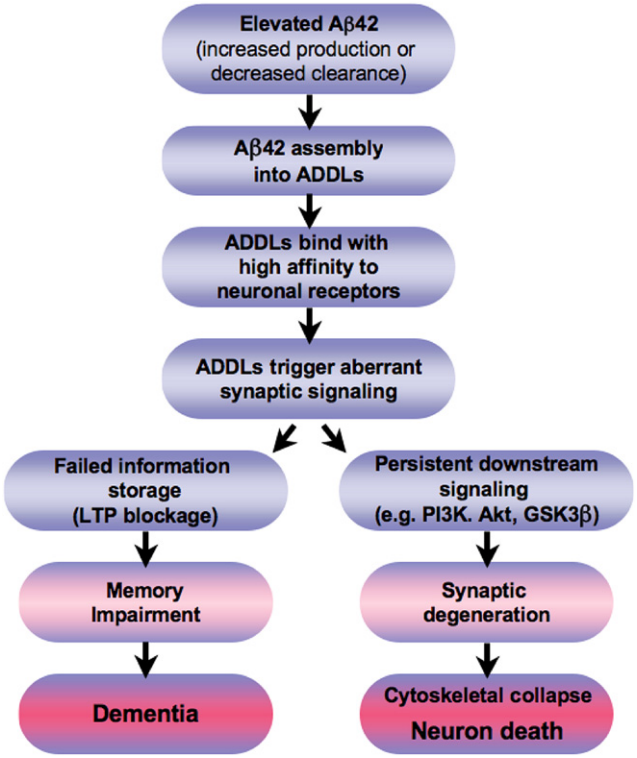

Fig. 1. Key elements of ADDL hypothesis.

2. ADDL formation and structural characteristics

2.1. ADDL preparation

The original protocol for preparing ADDLs involved incubation of 75 μM Aβ1–42 with 2.5 mole percent clusterin in pH 6.8 PBS at 22 °C for 48 h followed by centrifugation at 14,000 g to remove any large aggregates (Krafft et al., 1998; Lambert et al., 1998; Oda et al., 1995). In these experiments, clusterin suppressed fibril formation and enabled an alternative assembly into oligomers. ADDLs were also formed in the absence of clusterin by incubating 50 nM Aβ1–42 in brain slice culture medium at 37 °C for 24 h or alternatively by diluting a 5 mM DMSO solution of Aβ1–42 into cold F12 cell culture medium to 100 μM, incubating at 4 °C for 24 h and centrifuging at 14,000 g (Lambert et al., 1998). This latter protocol was further refined to eliminate conformational or aggregation state heterogeneity associated with different batches of synthetic peptide by monomerizing the lyophilized solid peptide in hexafluoroisopropanol (HFIP). Vacuum removal of the HFIP, after aliquoting the monomerized peptide into smaller, single use quantities, generated Aβ films that were dissolved in anhydrous DMSO immediately prior to use (Chromy et al., 2003; Dahlgren et al., 2002; Klein, 2002; Lambert et al., 2001). This protocol has been widely used, with Dahlgren et al. (2002) alone having been cited more than three hundred times. In spite of the popularity of this preparation, studies by Hepler et al. (2006) have suggested that it contains predominantly higher order structures with molecular weights greater than 150 kDa. When analyzed by SDS-PAGE, these larger structures readily disaggregate into lower molecular weight oligomers. Because the standard ADDL preparation contains a preponderance of large structures in solution, it is important to deploy lower, more physiologic concentrations of Aβ1–42 monomer for ADDL assembly. Using 1–5 nM peptide, ADDLs assemble in tissue culture media and can be detected as puncta, decorating dendritic spines of cultured hippocampal neurons, as illustrated in Fig. 2 (Krafft, Jerecic, McEntee, 2010 unpublished data). Experiments of this type show that ADDL formation can occur whenever the concentration of free (uncomplexed) Aβ1–42 monomer exceeds 0.5 nM.

A number of other preparations containing Aβ oligomers have been described in the literature, including SDS-stabilized dodecamers referred to as globulomers (Barghorn et al., 2005b; Gellermann et al., 2008), oligomers contained in conditioned media from APP-overexpressing 7PA2 CHO cells (Walsh et al., 2002), dodecamers obtained by extraction from Tg2576 mouse brain tissue referred to as Aβ*56 (Lesne et al., 2006), and very large oligomeric structures known as amylospheroids, formed from very high Aβ peptide concentrations in the presence of fibril blockers (Hoshi et al., 2003; Noguchi et al., 2009). In addition to these characterized preparations, a number of published studies have shown that treatment with relatively low concentrations of monomeric Aβ1–42 clearly leads to *in situ* formation of ADDLs (Gong et al., 2006; Puzzo et al., 2005, 2008; Levine, 2004).

2.2. ADDL structure

As mentioned earlier, ADDLs are, by definition, the neurotoxic subset of Aβ1–42 oligomers, however, the precise structure of the physiologically relevant assemblies is not known. Strong evidence has been published by a number of laboratories supporting the

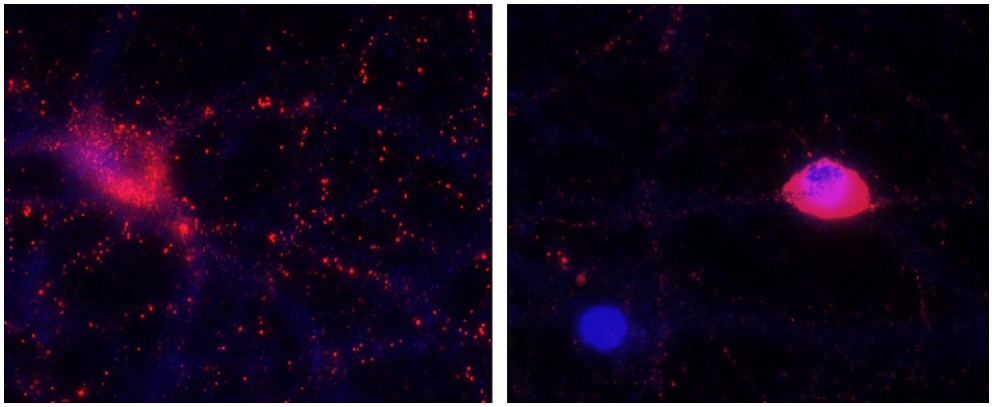

Fig. 2. ADDLs formed from 1 nM Aβ1–42 in neurobasal media and incubated with 17DIV rat hippocampal neurons for 30 min (left). DMSO control (right). Nuclei visualized with Hoechst stain; ADDLs detected with ADDL-selective mAb ACU-954 and Cy5-labeled secondary antibody.

proposition that dodecameric structures are the relevant neurotoxins. In 2003, our laboratories (Gong et al., 2003) demonstrated the presence of dodecamers in AD brain tissue extracts and showed that ADDL levels in AD brain were elevated more than 70-fold compared with brain tissue from age-matched non-demented individuals. Lesne et al. (2006) demonstrated that the appearance of dodecameric Aβ*56 in Tg2676 mice coincided with the onset of behavioral impairment, and Barghorn et al. (2005b) demonstrated that dodecameric globulomers exhibit postsynaptic binding and LTP blocking capability identical to ADDLs. More recent studies of Aβ1–42 oligomerization by Bernstein et al. (2009), using ion mobility coupled with mass spectrometry, demonstrated that Aβ1–42 forms dodecamers as the terminal oligomers, and unlike similar experiments with Aβ1–40, no stable smaller oligomers (e.g. dimers) could be observed.

Recent experiments published by Noguchi et al. (2009) demonstrated the presence of large oligomeric amylospheroids (ASPDs) in 100 kDa retentate fractions from homogenized AD brain tissue. These isolated ASPDs were neurotoxic and exhibited presynaptic binding, in contrast to ADDLs which bind to post-synaptic sites. The authors, however, did not describe comparative experiments using fractions containing oligomers smaller than 100 kDa. Their conclusions were also based on blotting procedures involving boiling, known to alter protein conformation and affect the immunoreactivity of Aβ species bound to the nitrocellulose. Lastly, the relevance of ASPDs to AD symptoms or pathology is not obvious, in view of the fact that these large structures have not been shown to assemble in vitro when low physiologic concentrations of Aβ (0.5–5 nM) are used.

Several recent studies by Townsend et al. (2006b) and Shankar et al. (2007, 2008) have suggested that Aβ dimers and trimers are the synaptotoxic structures, based on studies involving the use of 7PA2 cell culture derived material. While the published results may be consistent with the interpretation that Aβ dimers and trimers are the toxic species, the analysis carried out by these investigators cannot exclude the circumstance that larger oligomeric species are present in the 7PA2 media. Their analysis utilized antibodies 3g3 and 2f12, for which the recognition epitopes are Aβ33–40 and Aβ33–42, respectively. Because the hydrophobic Aβ C-terminus is buried within the oligomer core (Urbanc et al., 2004), it is likely to be poorly accessible to these antibodies when Aβ is assembled into oligomers larger than trimer, thereby compromising Western blot detection of larger assemblies (e.g. dodecamers). It is also clear that 3g3 and 2f12 cross-react with non-Aβ 7PA2 proteins, which migrate comparably on SDS with the expected migration of intermediate size oligomers (Walsh et al., 2005). Moreover, it is impossible to rule out the presence of larger oligomers in 7PA2 media, because all studies published on 7PA2-derived oligomers since 2005 have depicted Western blots cut off above 30 kDa.

We would also point out the possibility that solubilization of lyophilized 7PA2 peptide extracts in hot buffer immediately prior to gel analysis alters the conformational and assembly state integrity of Aβ species, thereby precluding definitive assessment of native oligomer size. It is quite possible that subjecting monomeric Aβ42 peptide to identical lyophilization and solubilization conditions would generate similar Western blot characterization results, but no such comparison experiment has been published.

In summary, while the overall conclusion that ADDLs impair synaptic plasticity and memory is supported by the results of many researchers, definitive results demonstrating the exact nature of the synaptotoxic species have yet to be reported.

3. Biological activities of ADDLs

Oligomers of Aβ were first observed by Roher et al. in 1991 during size exclusion chromatographic purification of Aβ from AD brain tissue, which generated fractions containing Aβ trimers, dimers and monomers (Roher et al., 1991). However, neurotoxicity experiments were described only for the purified monomer fraction and formic acid re-solubilized amyloid plaque core protein (APCP), both of which caused chick neuron cell death. The greater APCP toxicity was attributed to non-Aβ plaque components thought to be present in the APCP samples. A number of subsequent studies also mention Aβ oligomers, but none of these studies include experiments that characterize oligomer biological activity (Frackowiak et al., 1994; Kuo et al., 1996; LeVine, 1995; Podlisny et al., 1995; Roher et al., 1993; Vigo-Pelfrey et al., 1993). In 1996, Roher et al. described experiments involving biophysical characterization and assessment of cell culture activity for Aβ dimer, fractionated from AD brain or from incubation of synthetic Aβ 1–42 for (Roher et al., 1996). Atomic force microscope analysis revealed small oblong globular structures with Z-heights in the 3–4 nm range. Surprisingly, neither Aβ monomer or Aβ dimer were toxic to cultured primary neurons, however, both induced substantial toxicity when added to primary neurons co-cultured with microglia cells (Roher et al., 1996).

As mentioned earlier, Lambert et al. (Krafft et al., 1998; Lambert et al., 1998) were the first to describe neurotoxic activity of soluble globular Aβ oligomers (ADDLs), demonstrating potent toxic effects in cultured hippocampal neurons and CNS slice cultures. These studies were also the first to demonstrate that ADDLs could block

long term potentiation (LTP), and this key activity of ADDLs has since been corroborated in a number of synaptic plasticity models by many laboratories (Cerpa et al., 2008; Hsieh et al., 2006; Knobloch et al., 2007; Lesne et al., 2006; Li et al., 2009; Shankar et al., 2007; Smith et al., 2009; Townsend et al., 2006b; Venkitaramani et al., 2007; Walsh et al., 2002; Wang et al., 2002, 2004b). The demonstration that potent synaptotoxicity was associated with non-fibrillar Aβ assemblies was precedent setting in two respects. First, it solved a number of puzzling observations that could not be explained by invoking fibril/plaque toxicity, and second, it established a new paradigm for evaluating mechanisms by which other amyloidogenic proteins exert their toxic effects.

Since the discovery of ADDL neurotoxicity, a large number of publications have described results relevant to the question "Can ADDLs account for the major facets of AD neuropathology and symptomatic deficits?" Here we discuss results relevant to five emerging aspects of AD: selectivity of neuron loss, synaptic loss and dendritic spine effects, neuronal signaling receptor involvement, neuronal signaling pathways, and recently implicated insulin pathways.

3.1. Selectivity of neuron loss

Perhaps the most remarkable characteristic of AD pathology is the exquisite selectivity of cell loss, centered primarily on hippocampal CA1 and entorhinal cortex neurons, olfactory neurons and a small proportion of cortical neurons. Lambert et al. first described selective ADDL-induced, developmentally-dependent hippocampal neurotoxicity in brain slice cultures (Lambert et al., 1998), and these results were extended by Kim et al., who demonstrated that ADDLs killed a majority of CA1 neurons while sparing a major subpopulation of CA3 neurons (Kim et al., 2003). Fibrillar aggregates were unselective, killing CA1 and CA3 neurons with equal facility. Neurons in cerebellar slice cultures were unaffected by ADDL treatment, but suffered extensive death when treated with fibrils. Selectivity also was manifest with respect to cellular signaling pathways, as ADDLs had no effect on neurons in brain slices from *fyn* knockout mice (Lambert et al., 1998).

3.2. Synaptic loss and dendritic spine effects

Abnormalities in synapses from AD tissue were first observed in 1967 by Gonatas et al. (1967) and, since then, many studies have reinforced the concept that synapse loss is a fundamental characteristic of AD (recently reviewed by Arendt, 2009). Electron microscopy studies (Davies et al., 1987; Dekosky and Scheff, 1990; Gibson, 1983; Gonatas et al., 1967; Scheff et al., 1990, 2007) and immunocytochemical and biochemical analyses of synaptic marker proteins in AD and biopsy brain tissue (Dickson et al., 1995; Heinonen et al., 1995; Honer et al., 1992; Masliah et al., 1989; Terry et al., 1991) clearly demonstrate that synapse loss occurs early in the basal forebrain and neocortex, and it is the single AD pathology characteristic that best correlates with the severity of cognitive impairment (Hamos et al., 1989; Heinonen et al., 1995; Lassmann et al., 1992; Masliah et al., 1995; Perry et al., 1978). Mucke and coworkers measured significant synapse loss in transgenic mice that overexpressed wt hAPP (Mucke et al., 2000), a noteworthy observation in view of the absence of plaque or fibrillar pathology. Many studies have documented changes in synapse-associated molecules in AD tissues, including presynaptic components syntaxin, GAP-43 and SNAP-25 (Davidsson and Blennow, 1998; Masliah et al., 2001; Sze et al., 1997, 2000), postsynaptic molecules drebrin and neurogranin (Chang et al., 1997; Davidsson and Blennow, 1998; Harigaya et al., 1996; Hatanpaa et al., 1999), and a large number of synaptic vesicle components (Arendt, 2009).

There is good evidence to suggest that spine changes in AD are directly related to elevated Aβ secretion and consequent ADDL formation (Hsieh et al., 2006; Lacor et al., 2007; Lanz et al., 2003; Shankar et al., 2007; Shrestha et al., 2006). A recent study utilized Sindbis virus mediated APP overexpression to generate localized elevated Aβ levels in subsets of CA1 hippocampal slice neurons, the spine morphology effects of which were evaluated by imaging EGFP that was more broadly expressed via a second Sindbis virus (Wei et al., 2010). This study demonstrated that dendritically secreted Aβ reduced spine density at dendrites of proximal neurons that did not overexpress APP, while spine density was unchanged at more distant neurons. Parallel experiments infecting CA3 neurons with an APP/tomato virus demonstrated that Aβ overexpressed by axons also reduced spine density of proximal CA1 neurons. The reduction of spines by proximal elevation of Aβ could be prevented by blocking sodium channels with tetrodotoxin, blocking NMDA receptors with AP5, or by blocking nicotinic acetylcholine receptors (nAChR) with α-bungarotoxin. The protective effects of tetrodotoxin and α-bungarotoxin were shown to be mediated by reducing Aβ production, while the effects of the NMDA antagonist AP5 involved blockage of NMDA signaling. Exogenously administered ADDLs had identical effects on spine density. Elevated secreted Aβ or exogenously added synthetic ADDLs were also shown to prevent activity-dependent spine enlargement using a chemical induced LTP (cLTP) protocol. In viral-mediated APP overexpression experiments, only proximal neuron cLTP-induced spine enlargement was prevented, while more distant neurons exhibited normal cLTP-induced spine enlargement. These experiments clearly implicate Aβ as the cause of AD-associated changes to dendritic spines and synapses (Wei et al., 2010).

3.3. Neuronal signaling – receptors

A large and convoluted body of literature on neuronal signaling activities of Aβ oligomers has accumulated over the past decade, and it is safe to conclude that not all reported activities are relevant to ADDL-triggered memory impairment and neurodegenerative AD pathology, and in some instances observations and interpretations are mutually exclusive. To streamline the discussion, we will focus primarily on results obtained with primary hippocampal neurons, hippocampal slices or animal models. We will not be discussing studies employing high Aβ concentrations, which are known to generate large heterogeneous structures (>150–1000 kDa) (Hepler et al., 2006). These structures may exhibit different and perhaps irrelevant activities compared with smaller oligomers (3–12mers) that exist in AD and Tg AD mouse model brain tissue.

The single most relevant and consistently reported signaling abnormality triggered by ADDLs is blockage of long term potentiation, first published in 1998 (Krafft et al., 1998; Lambert et al., 1998). These early findings were validated by Wang et al. in 2002 (Wang et al., 2002) and, subsequently, numerous studies have confirmed that ADDLs interfere with LTP (Klyubin et al., 2004; Knobloch et al., 2007; Puzzo et al., 2008; Smith et al., 2009; Townsend et al., 2006b; Walsh et al., 2002; Wang et al., 2004a,b) and, in particular, with NMDA-dependent LTP (Chen et al., 2002). The initiating molecular interactions between ADDLs and neurons have not been delineated, however, a number of studies point to the involvement of NMDA receptors (Lacor et al., 2004; Li et al., 2009; Wang et al., 2004a). Memantine, an uncompetitive NMDAR antagonist, blocked the effects of ADDLs in cultured hippocampal neurons (De Felice et al., 2007a), while *in vivo*, it has been shown to reduce ADDL-induced memory dysfunction (Martinez-Coria et al., 2010). However, memantine itself disrupts learning and memory

(Creeley et al., 2006), and a recent study showed dose-dependent inhibition of LTP by memantine and increased perseveration and approach errors in the rat ALCR behavioral paradigm (Klyubin et al., 2009). Other recent studies have demonstrated that NMDAR antagonists ifenprodil and Ro 25-6981, which are specific for the NR2B subunit, protected against ADDL effects (Ronicke et al., 2010), while the inhibitors NVP-AAM077 or UBP141, which preferentially target NR2A and NR2C/D, respectively, did not (Hu et al., 2009; Klyubin et al., 2009). These results suggest that a subpopulation of NR2B-containing NMDARs must be activated in order for ADDLs to impair LTP, but they do not mandate that ADDLs directly interact with NR2B.

Evidence for involvement of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluR2 in mediating ADDL effects has been published recently (Zhao et al., 2010). ADDL binding was shown to localize on dendritic spines, and ADDL co-localization occurred to the greatest extent on spines lacking GluR1 and expressing GluR2. Treatment of hippocampal neurons for 30 min with glutamate, AMPA, insulin or IGF-1, all known to down-regulate AMPA receptors, resulted in significantly reduced ADDL binding (Ronicke et al., 2010). ADDL treatment also resulted in rapid endocystosis of ADDLs and AMPA receptors (Cottrell et al., 2004). AMPA receptors co-localize with CPG2, which localizes specifically at the postsynaptic endocytic zone of excitatory synapses and plays an important role in activity-dependent glutamate receptor endocytosis. Treatment with AMPA receptor antagonists reduced the extent of ADDL binding and prevented ADDL-induced loss of AMPA receptors (Zhao et al., 2010). Calcineurin inhibitors were also effective in preventing AMPAR endocytosis. The involvement of calcineurin activity in propagating the effects of ADDLs or soluble Aβ has been observed in a number of other studies (Abdul et al., 2009; Chen et al., 2002; Shankar et al., 2007; Wu et al., 2010), and treatment with calcineurin inhibitors reverses memory deficits in Tg AD model mice (Dineley et al., 2007; Taglialatela et al., 2009). The activation of calcineurin results in dephosphorylation of the transcription factor NFATc4, resulting in its translocation to the nucleus. The specific transcriptional targets of NFATc4 in neurons are not known.

There is considerable evidence for the involvement of tumor necrosis factor alpha (TNFα) and its receptor TNFR1 as mediators of LTP deficits triggered by ADDLs. The ability of TNF itself to interfere with LTP has been known for nearly two decades (Albensi and Mattson, 2000; Tancredi et al., 1992), and it appears that some TNF-triggered synaptic effects involve perturbation of AMPA receptor trafficking (Stellwagen et al., 2005). TNF impacts glutamatergic synaptic transmission in a number of other ways, which have been reviewed recently (Pickering et al., 2005). Oligomeric Aβ can stimulate TNF production by astrocytes (Akama and Van Eldik, 2000; Hu et al., 1998; White et al., 2005) and by microglial cells (Chen et al., 2005; Floden and Combs, 2006; Jiao et al., 2008; Pan et al., 2009; Sondag et al., 2009), and results from a number of studies support a model in which glial-derived TNF, interacting with neuronal TNF receptors, is responsible for LTP blockage and memory deficits. It is possible that ADDLs interact with TNFR1 directly to propagate similar signaling abnormalities, but it is also possible that ADDLs interact with GPCRs that act via $G_{\alpha}i$ and $G_{\beta\gamma}$, which can trigger many of the same signaling pathways.

3.4. Neuronal signaling – pathways

There are a number of reports citing activation of c-Jun N-terminal kinase (JNK) and the mitogen activated kinase p38 after treatment of neurons with oligomeric Aβ, and blockage of either of these kinases abrogates the LTP blockade by ADDLs. As mentioned earlier, the protein phosphatase calcineurin is activated by ADDLs, and its inhibition also prevents the signaling and memory malfunction triggered by ADDLs. Glycogen synthase kinase 3β (GSK-3β) activity, responsible for the aberrant tau phophorylation associated with AD, is increased by ADDL treatment, and this activity is likely to contribute directly to LTP inhibition, in view of the ability of elevated GSK-3β activity alone to block LTP.

There are conflicting reports with respect to the impact of ADDLs on PI3K/Akt signaling. Earliest links between Aβ and PI3K activity suggested an antagonistic relationship, with multiple reports indicating that stimulation of the PI3K pathway blocks aspects of Aβ-related toxicity. For example, Kihara et al. (2001) reported in 2001 that stimulating α7nAChRs in mature cultures of cortical neurons blocked Abeta toxicity through a mechanism that was sensitive to the PI3K inhibitor wortmannin and the Src family inhibitor PP2. Nicotinic receptors were found to form physical complexes with PI3K and Fyn, both of which, in contrast, also have been linked to the deleterious impact of ADDLs (Lambert et al., 1998). Analogous neuroprotection has been found using the human neuronal cell line SHSY5Y, shown earlier to undergo AD-type tau phosphorylation and apoptosis by Lambert et al (Lambert et al., 1994) in response to toxic Aβ preparations. The hyperphosphorylation of tau is inhibited by stimulation with erythropoietin (Sun et al., 2008), an agonist in these cells of the PI3K/Akt pathway which leads to inhibition of GSK3β. Interestingly, the Alzheimer's therapeutic drug Donepezil, considered an anticholinesterase agent, in fact prevents Aβ-induced apoptosis in SHSY5Y cells by also stimulating PI3K activity (Arias et al., 2005), similar to protection observed with nicotine. Conversely, inhibitors of PI3K did not affect Aβ-induced death in these cells, consistent with a previous study showing that PI3K overactivation had no affect on Aβ-induced toxicity (Wei et al., 2002). It should be noted that in these and other neuroprotection studies, the systems have comprised a wide variety of cell lines and types, with the readout often being apoptosis. It is unclear and it is probably unlikely that apoptosis is the direct consequence of oligomer attachment to neurons (Kim et al., 2003). The protection afforded by stimulation of PI3K pathways suggests that Aβ could act by inhibiting PI3K activity, however, the impact appears to be indirect.

The apparently contradictory results involving Aβ toxicity and PI3K signaling may reflect differences in readout rather than incompatible data. For PI3K signaling associated with mGluR5 receptors, both agonists and antagonists show protection against Aβ-toxicity, even in the same hippocampal culture model. However, agonists protect against apoptosis (Liu et al., 2005), which may actually be initiated by factors released by glial cells, while the antagonists protect against synaptotoxicity (Wang et al., 2004b), a direct neuronal effect of ADDLs. Results with the mGluR5 pathways are especially notable given the recent description of a new mechanism of ADDL synaptotoxicity involving the induced clustering of mGluR5 (Renner et al., 2010). Quantum-dot measurements of ADDL and mGluR5 surface-time diffusion in living neurons show ADDLs act essentially as extracellular scaffolds, triggering toxicity by causing the clustering, immobilization, and localized hyperactivity of mGluR5 receptors.

Newly emerging results strongly suggest that ADDL synaptotoxicity and behavioral dysfunction may, in fact, be mediated by *stimulation* of PI3K pathways. Initial support was obtained by findings that upregulation of AD-type pTau in cells exposed to synthetic or brain-derived ADDLs could be prevented by inhibitors of PI3K as well as inhibitors of Src PTKs (De Felice et al., 2008). Upregulation of pTau by stimulation of PI3K signaling is consistent with the report by Bhasker et al. that pathological cell cycle events are stimulated by ADDLs in post-mitotic cortical neurons via PI3K-mediated signaling (Bhaskar et al., 2009). AD-type pTau upregulation earlier was shown to be spontaneously upregulated during

mitosis (Pope et al., 1994). Interestingly, the Bhasker study also implicates ADDL-stimulated PI3K activity in dendritic atrophy, which potentially is mediated by the mGluR5 clustering mentioned earlier.

A direct link of PI3K hyperactivity to plasticity and memory failure has been reported in very recent studies of transgenic Drosophila (Chiang et al., 2010) and transgenic mice (Caccamo et al., 2010). Flies expressing aggregated human Aβ42 exhibited excessive LTD and PI3K activity, while inhibiting PI3K activity (by gene silencing as well as pharmacologically) prevented transgene-induced promotion of LTD and the associated memory failure. Analogously, in the widely used triple transgenic mouse AD model, memory deficits measured by Morris water maze by Caccamo et al. (2010) were blocked by reduction in mTOR signaling using rapamycin. This effect is consistent with their results showing that mTOR signaling is elevated by Aβ in cell biology experiments. Physiological signaling is short-lived, whereas toxic signaling due to ADDLs appears to be long-lived. Rapamycin, an already FDA approved drug, also reduced Aβ-induced tau pathology, further supporting its possible promise for Alzheimer's therapeutics. It is clear, however, that targeting an essential signal transduction enzyme presents significantly more challenges than targeting pathological molecules, e.g. ADDLs, which are restricted to disease states.

3.5. ADDLs and insulin signaling

Perhaps the most intriguing example of signaling interactions can be found in the relationship between ADDLs and CNS insulin signaling. Brain insulin signaling is now known to participate not only in regulation of energy metabolism but to play a synaptic role that modifies plasticity and is linked to memory function. In a culture model, spontaneously elevated intracellular Aβ, presumably oligomeric, was shown to block the ability of insulin to stimulate PDK-dependent activation of Akt (Lee et al., 2009). These findings are consistent with reports that PDK-Akt association and activated pAkt levels are reduced in AD brain (Mannella and Brinton, 2006). In addition, ADDLs were unable to reverse already activated PI3K or Akt. This uncompetitive activation may be a factor in the protective effects against ADDL toxicity, although it is still difficult to sort out how multiple influences that stimulate and inhibit pathways combine to establish outcomes.

The negative impact of ADDLs on neuronal insulin signaling provides a substantive basis at the molecular level for the emerging notion that AD in many respects resembles a "type 3 diabetes," in which the insulin-resistant organ is the brain. Interestingly, the insulin-ADDL interplay is a double-edged signaling sword – synaptic insulin-R signaling is prevented by ADDLs, while toxic ADDL signaling is prevented by insulin. Measurements of insulin R-PTK activity in hippocampal neurons show the rapid inhibition by ADDLs at very low doses (Zhao et al., 2008). Associated with this inhibition is an upregulation of Akt phosphorylation at ser473, a modification associated with insulin resistance and neurodegenerative disease. Prior ADDL exposure also results in loss of the ability of insulin signaling to promote clearance of ADDLs. In essence, this resembles a positive feedback response that could underlie an increase in pathology.

A second protective effect of insulin, besides helping to remove ADDLs, is a major down-regulation of ADDL binding, which shields synapses from ADDL toxicity. At sub-maximal doses of insulin, the PPARγ agonist rosiglitazone (Rz) enhances the protective signaling effect (De Felice et al., 2009), likely a basis for the reported beneficial effects of Rz on cognition. Although Rz has been minimally effective in clinical trials, it is likely that the drugs have been administered too late, especially given the ability of ADDLs to down-regulate insulin signaling. Significantly, down regulation of ADDL binding by insulin is dependent on R-PTK activity (Zhao et al., 2009). Thus, protection is not a simple competition between insulin and ADDLs for the same binding proteins, but rather a putative removal of specific ADDL binding proteins from the surface. The nature of those proteins is still under investigation, although a number of candidates have been suggested, including the insulin receptor itself, as well as NMDA-Rs, AMPA-Rs, prion proteins, and mGluR5 receptors.

As mentioned before, while insulin is down-regulating ADDL receptors, ADDLs do the same for insulin receptors. The cell biological findings provide a basis for decreased dendritic insulin receptors observed in AD neuropathology (Moloney et al., 2010). Whether insulin or ADDLs win the battle in the synaptic struggle for survival appears to depend on which signal is robustly active before the other. The conflict between protective insulin and toxic ADDLs has led to the hypothesis that decreased CNS insulin signaling, which is not uncommon with aging, is an important risk factor for AD.

4. ADDL-directed therapeutic strategies

4.1. ADDL assembly-directed approaches

On first inspection, the prospects for successful discovery of small molecules to prevent assembly of Aβ42 into ADDLs might appear to be slim, given the challenging requirement to block peptide-peptide interactions, and the long record of futility among fibril blocker discovery programs throughout the 1990s. Nevertheless, several papers have described promising molecules with potencies already exceeding the best fibril inhibitors. One study involved screening of a library containing various functionalized cyclodextrins (Yu et al., 2002), inspired by early observations that cyclodextrin could attenuate the neurotoxicity of Aβ42 injected directly into rat hippocampus (Waite et al., 1992). An early analog containing aminomethylfuranyl groups at each 6-position of the cyclodextrin sugar blocked ADDL assembly with an IC_{50} of 250 nM in a dot-blot assay using an ADDL-selective polyclonal antibody (Wang et al., 2004c). The analogous functionalized α-cyclodextrin analogue PAF6 blocked assembly with an IC_{50} of 60 nM, more than twice as potent as any fibril blocker reported in the peer-reviewed or patent literature. These cyclodextrin analogues do not represent particularly good drug candidates due to sub-optimal blood-brain barrier penetration, yet their discovery does highlight the feasibility of interfering with ADDL assembly.

More recently, a series of substituted aromatic compounds was evaluated for ADDL blocking ability, and several molecules exhibited reasonable activity. The most potent compound was 2-hydroxy-3-ethoxybenzaldehyde, with an IC_{50} of ~3 μM. Although not particularly potent compared with the cyclodextrin analogue PAF6, these small organic compounds also could block the assembly of Aβ42 into fibrils (De Felice et al., 2004). Another study demonstrated that the standardized gingko biloba extract EGb761 reduced the level of small oligomers at a concentration of 10 μg/mL, a level that coincided with protection against ADDL-induced toxicity in several different PC12 assays, including glucose uptake and apoptosis (Yao et al., 2001). A series of ADDL blocking spirosterols also have been described, with the most potent analogs inhibiting neurotoxicity at 30 μM, when cells were treated with 10 μM Aβ42 (Lecanu et al., 2004). These sterols appear to promote formation of higher order aggregates and may block toxicity by binding to higher order aggregates, effectively masking surface epitopes involved in binding to cell surface receptors.

A number of cyclodextrin compounds, first intended to be possible fibril blockers were reported to block ADDL formation, the

most potent of these having an EC_{50} of 0.63 μM (Wang et al., 2004c), and a 2001 paper described the ability of dietary curcumin to block oxidative damage when ADDLs were administered ICV in a rat model (Frautschy et al., 2001). Results from a subsequent study suggest that curcumin may exert its protective effects by blocking ADDL assembly (Yang et al., 2005), however, the *in vitro* toxicity studies utilized N2a and SHSY-5Y cells, neither of which exhibit the highly specific, high affinity dendritic spine binding by ADDLs, which is characteristic of well developed, 14-21 DIV primary hippocampal neurons (Lacor et al., 2007). Another study reported on the ability of both nicotine enantiomers to slow Aβ40 fibril formation and to influence the distribution of Aβ40 oligomers (Moore et al., 2004). Effects of nicotine on Aβ42, which has a greater aggregation propensity, have not been reported. Two compounds previously described by Sankyo Co., Ltd. (Nakagami et al., 2002) as fibril blockers also blocked formation oligomers when added to the APP-overexpressing 7PA2 CHO cells, and the resulting culture medium did not block LTP when added to hippocampal slice cultures. One compound was effective at 9.3 μM and the other at 100 μM.

Another recent paper reported that scyllo-inositol could prevent memory impairment or LTP compromise by cell-derived Aβ oligomers (Townsend et al., 2006a). Originally, scyllo-inositol had been thought to exert its effects by preventing aggregation of Aβ. Instead, it appears that scyllo-inositol binds specifically to Aβ trimers, perhaps masking critical surface epitopes involved in dodecamer assembly or binding interactions with neuronal receptors. Taken together, all of these studies serve as promising indicators that effective small molecule assembly blockers may emerge as effective anti-ADDL drugs.

Neurochem's Alzhemed [tramiprosate, 3APS], which recently failed to demonstrate efficacy in a large Phase III clinical study (Catalano et al., 2006), had been reported to bind the N-terminus of Aβ, which normally interacts with glycoaminoglycans. In Tg AD mice, Alzhemed was effective at preventing plaque formation and this led to effective prevention of plaques in APP-overexpressing transgenic mice. The molecule also has been reported to interfere with ADDL formation, although there are no supporting data to substantiate this.

4.2. ADDL-directed immunotherapy approaches

In principle, immunotherapy directed towards Aβ monomer could interfere with ADDL formation, depending upon the capability of anti-Aβ antibodies to obscure those monomer regions that mediate assembly, or the ability to lower Aβ42 concentrations substantially to reduce ADDL assembly kinetics. Anti-Aβ monomer antibodies also could block ADDL-receptor interactions by obscuring key epitopes on the ADDL surface. Realization of either scenario undoubtedly will depend upon the quantity, potency and specificity of Aβ-binding antibodies delivered or generated by a particular approach.

The earliest Aβ-directed immunotherapy studies involved vaccination of hAPP transgenic PDAPP mice with aggregated Aβ42 leading to reduction of brain Aβ deposits and slower development of pathology (Schenk et al., 1999). A subsequent study demonstrated that passive vaccination with anti-Aβ antibodies (Bard et al., 2000) also could reduce Aβ deposits. In this study, two monoclonal and one polyclonal antibody [3D6, 10D5, PabAb1–42] lowered Aβ, whereas two other Aβ monoclonal antibodies [21F12, 16C11] and the Ig-isotype-matched control antibody did not reduce Aβ levels. The efficacious anti-Aβ antibodies co-localized with plaques in unfixed PDAPP brain cryosections, leading these authors to suggest a mechanism for Aβ clearance involving initial transport of anti-Aβ antibodies across the blood–brain barrier, subsequent binding of the antibodies to microglial Fc receptors, and eventual phagocytosis of Aβ deposits. Studies by other groups have confirmed that both active and passive vaccination lead to effective Aβ clearance (reviewed in Brendza and Holtzman, 2006).

The first reports that vaccination could confer behavioral benefits were published in late 2000. TgCRND8 mice vaccinated with Aβ42 exhibited improved performance in a reference memory version of the Morris water maze test (Janus et al., 2000), while vaccination of Tg2576 or PSAPP mice with Aβ42 enhanced performance in a radial-arm maze (Morgan et al., 2000). In both studies, behavioral improvement occurred without significant reduction in Aβ levels, suggesting that plaque clearance was not required. These studies were the first to support the concept that the behavioral effects might be due to interference with ADDLs, rather than clearance of plaques. Several subsequent studies provided further support for this concept by demonstrating that single injections of anti-Aβ antibodies improved learning behavior only 24 h after administration, and without coincident reduction of total Aβ levels (Dodart et al., 2002; Westerman et al., 2002). Since these studies were published, a number of studies involving active vaccine constructs or Aβ specific monoclonal antibodies have confirmed the ability of Aβ-directed immunotherapy to reduce Aβ plaques and deposits, yet it is clear that plaque clearance alone does not improve behavior or cognition (Dodart et al., 2002; Kotilinek et al., 2002).

The first human clinical trial of an Aβ-directed vaccine [AN1792] involved pre-aggregated Aβ42 and the adjuvant QS-21, but the trial was terminated in early 2002 when four patients developed meningoencephalitis, which eventually was manifest in 18 of 298 treated patients (Ferrer et al., 2004; Nicoll et al., 2003; Orgogozo et al., 2003; Senior, 2002). A recent analysis of post-mortem tissue from patients immunized with AN1792 revealed that effective clearance of plaques had occurred. There was no correlation between encephalitis and anti-Aβ antibody titer and it has been suggested that T cell activation in response to the self-immunogen, particularly the mid- and carboxy-terminal portion of the Aβ42 peptide, was responsible for the encephalitis (Monsonego et al., 2003). The safety concerns raised by this study have redirected most immunotherapy efforts towards passive immunization with humanized monoclonal antibodies. AAB-001 is one such antibody currently in Phase II clinical trials for the treatment of mild to moderate Alzheimer's disease (Black et al., 2010). Since AAB-001 recognizes an N-terminal epitope of the Aβ peptide, it is not likely to exhibit any binding preference for ADDLs over other forms of Aβ.

Several groups have described ADDL preferring antibodies. Lee et al. (2006) recently described a "conformation selective" monoclonal antibody [NAB61], which brought about significant improvement in learning and memory in Tg2576 mice. Further, Ma et al. (2006) demonstrated that treatment of Tg2576 mice with an anti-Aβ antibody [N-terminal epitope] reduced levels of phospho-tau, which correlated with reduction in ADDL levels detected in brain tissue extracts from treated animals. A 2007 study (Chauhan, 2007) used ICV administration of the oligomer-selective polyclonal antibody A11 (Kayed et al., 2003), which resulted in reduction of oligomer levels and plaque levels in the treated TgCRND8 mice. The extent of reduction and the duration of clearance were greater for A11 than for the fibril recognizing antibody AMY33 (Solomon et al., 1996), also delivered ICV (Chauhan and Siegel, 2002). Another study (Moretto et al., 2007) described a "conformation sensitive" antibody raised to a recombinant bacterial thioredoxin chimera in which a linear Aβ 1–15 tetramer was inserted into an active site loop. The antibody recognizes oligomeric Aβ and not Aβ monomer, but it also binds fibrils and other amyloidogenic proteins such as transthyretin, in a manner similar to A11. Stereotaxic injection into the hippocampus of Tg2576 mice resulted in virtually complete

plaque clearance within 7 days, and significant reduction in astrogliosis. A number of ADDL-selective monoclonal antibodies, described in a recent publication, exhibited potent ADDL blocking ability in primary neuronal cultures. These antibodies, selected for their ability to differentiate AD and control brain tissue, are the first examples of monoclonal antibodies generated by immunization with ADDLs, and they represent excellent prototypes for humanized antibodies that could be used to treat AD patients (Lambert et al., 2007).

To this end, a number of companies have disclosed efforts to discover and develop ADDL-preferring antibodies, including Abbott, Eisai/BioArctic, Wyeth, and Merck/Acumen. Abbott described a method for homogenous preparation of ADDL structures through inclusion of sodium dodecyl sulfate [SDS] (Barghorn et al., 2005a) supporting independent descriptions of the stabilizing properties of SDS on ADDL formation (Bitan et al., 2005). Several Abbott monoclonal and polyclonal anti-ADDL antibodies [e.g. 6G1, 8F5 and pAb5598] have now been described (Barghorn et al., 2005a,b). These antibodies bind to neurons in a manner consistent with previously described anti-ADDL antibodies (Klein et al., 2004) and efficiently block the inhibition of long-term potentiation produced by exogenous ADDL application (Barghorn et al., 2005a). Wyeth researchers have disclosed the results of a systematic analysis of the cognitive benefit of anti-Aβ antibody treatment in Tg2576 mice. In these studies, multiple antibodies with known linear epitopes were evaluated. Regardless of linear epitope, only antibodies that recognized ADDLs by Western blot analysis were effective in improving cognition in a contextual fear conditioning assay (Comery et al., 2005). Further, the ability to improve cognition by targeting ADDLs may occur independent of any notable reduction of overall Aβ levels as measured using standard techniques (Ma et al., 2006), suggesting that the most relevant species of Aβ for therapeutic intervention may represent a relatively minor population. As such, antibodies exhibiting a strong preference for ADDLs over monomer should be substantially more effective at neutralizing ADDLs than non-specific antibodies (Kinney et al., 2005). A very recent study from Merck scientists (Shughrue et al., 2010) evaluated a number of anti-ADDL antibodies, several of which exhibited high potency with respect to blocking ADDL binding to hippocampal slice cultures and primary hippocampal neurons. One antibody, ACU-954 was particularly effective, and could prevent ADDL-induced loss of dendritic spines.

The feasibility of ADDL specificity in an active vaccine is supported by the finding that immunization of rabbits with ADDL preparations results in anti-sera with ~1000-fold higher affinity for ADDLs over monomer, with excellent capability to prevent ADDL-induced toxicity in vitro (Lambert et al., 2001). These results suggest that, although ADDLs represent a minor component of total Aβ, it is a relatively immunogenic species. Thus, active immunization strategies can be envisioned that would allow for high specificity and immunogenicity against this Aβ component.

4.3. Therapeutic approaches targeting synaptic ADDL signaling

Significant changes in synaptic function and morphology have been attributed to ADDLs. Exposure of neurons to ADDLs in vitro leads to rapid changes in synaptic signaling and receptor surface expression (De Felice et al., 2007a; Hsieh et al., 2006; Lacor et al., 2007; Shankar et al., 2007; Snyder et al., 2005; Vitolo et al., 2002). Many of these changes can be reversed or reduced via application of known agonists or antagonists, demonstrating that pharmacological intervention can be therapeutic at the synaptic level.

Excitatory, glutamatergic synapses appear to be particularly vulnerable to the effects of ADDLs. ADDLs bind selectively to PSD95-positive dendritic spines (Lacor et al., 2004), and exposure of older hippocampal cultures to low concentrations of ADDLs results in loss of dendritic spines and shape alterations in remaining spines, as well as a selective loss of presynaptic glutamatergic terminals. The ADDL-mediated regression of spines can be reversed by washout (Shrestha et al., 2006), and in some cases appears to be transient, disappearing after two days in culture (Calabrese et al., 2007). Antagonists of NMDA and ACh receptors attenuate these structural regressions (De Felice et al., 2007b; Hsieh et al., 2006; Lacor et al., 2007; Shankar et al., 2007; Snyder et al., 2005), but some alterations remain. For example, treatment with the NMDAR antagonist memantine effectively blocked the ADDL-mediated decrease of drebrin in spines, but did not prevent ADDL binding to neurons (Lacor et al., 2007).

Rapid modification of intracellular calcium levels precedes the morphological changes in synapses and spines. DeFelice et al. report a 3.5-fold increase in intracellular calcium levels measured in the cell soma of dissociated hippocampal neurons [21DIV] within the first 20 seconds of ADDL exposure (De Felice et al., 2007a). This effect can be blocked by memantine. Longer exposure [hours to days] of organotypic hippocampal cultures or dissociated neurons to ADDLs results in a down-regulation of signaling molecule expression [including NMDAR and AMPARs] and a 27% decrease in intracellular calcium transients measured within the spines that do not regress (Calabrese et al., 2007; De Felice et al., 2007a; Hsieh et al., 2006; Lacor et al., 2007; Shankar et al., 2007; Snyder et al., 2005). The inhibitory effect of ADDLs on NMDAR-dependent long term potentiation (LTP) is consistent with its binding to excitatory synapses. ADDL-induced LTP-inhibition has been attenuated by pharmacological inhibitors of mGluR5, NMDARs, nAChRs, calcineurin, p38MAPK, JNK, cdk5, iNOS, superoxide, and TNFα (Chen et al., 2002; Hsieh et al., 2006; Puzzo et al., 2006; Snyder et al., 2005; Wang et al., 2004a,b). Although the sequence of events leading from ADDL binding to LTP inhibition is still unknown, targeting these molecular pathways should provide effective therapeutics.

Current strategies for treatment of AD aim to improve cognitive function by antagonizing NMDA receptor function or enhancing cholinergic transmission. Memantine, a moderate affinity, noncompetitive voltage dependent NMDA receptor antagonist, has been approved for treatment of moderate to severe AD (Chen and Lipton, 2006; Doody et al., 2004; Lipton, 2006). Consistent with its ability to attenuate some of the ADDL-mediated changes in synaptic morphology and function, this drug provides moderate symptomatic relief but does not modify disease progression appreciably. Partial inhibition may be ultimately unable to compensate for deficits caused by rising levels of ADDLs. Clearly, much about ADDL signaling and its impact on NMDARs remains obscure at this time.

Antagonists of mGluR5 block ADDL mediated inhibition of LTP (Wang et al., 2004b) and novel drugs targeting the metabotropic glutamate receptor 5 are currently under development. Activation of mGluR5 increases intracellular calcium levels by inducing calcium release from intracellular stores and stimulation of PKC, potentiation of L-type voltage dependent calcium channels, and activation of downstream signaling through cdk5and/or p38 MAP kinase. The first negative allosteric modulators of mGluR5 were developed at SIBIA-Novartis (Varney et al., 1999), and more potent analogues have been generated at Merck, Addex Pharmaceuticals/Johnson and Johnson, Roche and others. Consistent with its role in modulating neuronal function in many contexts, several different clinical indications are being pursued for these mGluR5 compounds including Alzheimer's disease, schizophrenia, anxiety, obesity and GERD.

Similarly, changes in intracellular calcium levels are intrinsic to multiple neurological diseases and are not expected to be specific to AD. Memory Pharmaceuticals, Inc has developed MEM 1003,

currently in phase II trials, a neuronal L-type calcium channel modulator that regulates calcium flow and reestablishes normal intracellular levels.

A number of ADDL-mediated signaling studies converge on the cAMP/PKA/CREB pathway. ADDLs inhibit glutamate- and BDNF-induced upregulation of CREB after 2 h of treatment, but do not themselves alter basal pCREB levels (Tong et al., 2001, 2004). This effect appears to be mediated by reduction of phosphorylation of docking proteins insulin receptor substrate-1 [IRS-1] and Shc isoforms, rather than interference with TrkB receptor activation. CREB is required for normal LTP function, and CREB signaling pathways have been proposed to underlie ADDL-mediated LTP inhibition (nitric oxide and the soluble guanylyl cyclase/cGMP/cGMP-dependent protein kinase pathway (Puzzo et al., 2006) as well as the Uch-1/proteasome/PKA pathway (Gong et al., 2006)). Rolipram, a PDE IV inhibitor that upregulates cAMP, rescues ADDL-mediated LTP inhibition and spine reduction (Shrestha et al., 2006; Vitolo et al., 2002) as well as behavioral deficits in an animal model of AD (Gong et al., 2004). CREB pathway targets have been explored as potential memory enhancing therapeutics (Tully et al., 2003). Memory Pharmaceuticals Inc. has developed MEM 1917 and other PDEIV inhibitors for AD treatments. Vernalis PLC [formerly Cita NeuroPharmaceuticals Inc] discovered CNP 1061, a soluble guanylyl cyclase agonist that activates CREB. Krenitsky Pharmaceuticals Inc. has reported on the discovery of KP544, a small molecule modulator of NGF and cAMP for treatment of MCI and AD.

Recent observations confirm that synaptic loss is the basis for the cognitive decline that is the hallmark of MCI and early AD pathology, and this observation shifts the therapeutic focus away from cell death and towards synaptic memory-related signaling pathways. Aβ42 accumulation and formation into ADDLs is another hallmark of MCI and early AD pathology, and ADDLs have been directly linked to alterations of synaptic memory-related signaling pathways. Initial changes in synaptic strength marked by ADDL-induced LTP failure are followed within hours by a persistent modification of synaptic signaling and synaptic morphology. Although the primary ADDL binding partners have not been characterized, prevention of ADDL binding to its target receptors or restoring 'early stage' aberrant synaptic signaling via pharmacological intervention is expected to halt development of AD pathology. Ultimately, the ability of pharmacological interventions to rescue ADDL-induced memory deficits will depend on the degree to which they can block ADDL-induced signaling events.

5. Future prospects

The ADDL-modified version of the amyloid cascade hypothesis now provides an excellent framework for continued mechanistic studies and for the critical translational research that will lead to selective ADDL-directed therapeutics. Within the next several years, ADDL-directed immuno-therapeutics, assembly blockers and receptor antagonists should emerge from current drug discovery and pre-clinical efforts to provide the first human testing of the ADDL hypothesis. It is also likely that entirely novel ADDL signaling antagonists will emerge, as the web of ADDL-triggered signaling becomes more fully understood.

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