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Alzheimer's amyloid-beta (Aβ) is an essential synaptic protein, not neurotoxic junk

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Review

Abstract. Despite a decade long universal publication in favor of the view on amyloid-β (Aβ) as Alzheimer's disease culprit (solely neurotoxic for neurons and brain tissue), current scientific evidence leaves little doubt that Aβ serves an essential role at synapse and in synaptic structure-functional plasticity that underlie learning and memory. Therefore, the change of Aβ biology in Alzheimer's disease (as well as in a number of other human pathologies, including cardiovascular disease, neuromuscular junction disorders, NPC and Down's syndrome) may represent a physiological mechanism to compensate for impaired brain structure or function. In our own recent study $A\beta_{1\text{-}40}$ rescued long term potentiation (LTP, a major model for activity-dependent CNS plasticity), while cholesterol synthesis inhibition abolished the restorative action of the Aβ peptide. This study confirms that Aβ protein is a functional player in synaptic structure-functional plasticity and in cholesterol neurochemical pathways. The article also calls for a need to critically re-evaluate a universal belief that transgenic mice with a transgene for amyloid-β protein precursor (AβPP) are a true model for Alzheimer's type neurodegeneration.

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INTRODUCTION

What Alois Alzheimer saw in early 1900s in brain samples from the first Alzheimer's disease (AD) case ever to be described in medical literature were senile plaques, composed of many components, including amyloid-β protein (Aβ) (Enserink 1998). Aβ (first described by Glenner and Wong (1984) is derived from the amyloid-β protein precursor (AβPP) *via* complex proteolytic pathway catalyzed by a number of secretases (Koudinova et al. 1999, Koudinova and Koudinov 2003). However, the short amino-acid sequence of Aβ (with $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ as the major species) allows easy synthesis of the peptide and explains why the vast majority of *in vitro* experimentation with Aβ is performed with the synthetic peptides. In the past, experimentation with Aβ were performed at very high peptide concentrations that would never occur physiologically or even in pathological conditions. Such *in vitro* studies yielded experimental data on Aβ fibril formation and its potential role in AD. Interestingly, despite the claimed abundance of Aβ in the AD brain, naturally occurring human Aβ was never purified in preparative condition for experimentation with natural protein.

Many years of intense research and millions of research dollars did not help to resolve the role for Aβ in AD. Conversely, in 1992 several reports showed that there is a soluble form of Aβ which is normally produced by cells in culture (implying that the secretion of soluble (s) Aβ is physiologic) and can be detected in plasma, cerebrospinal fluid (CSF) and brain tissue (Koudinova et al. 1999). In our own studies, we further showed that, in plasma and CSF, sAβ circulates as part of high density lipoproteins (HDL) and that sAβ is secreted by cells as an apolipoprotein constituent of lipoproteins (Koudinov and Koudinova 1997, Koudinov et al. 1994, 1996a, 2001a, Koudinova et al. 1996a). Other groups (referenced in Koudinov et al. 2001a) latter confirmed this in several reports.

AβPP processing (leading to Aβ-bearing C-terminal fragments) is strongly conserved in animals from insecta to mammalia, suggesting that sAβ is involved in very basic and important metabolic pathways (discussed in Koudinov and Koudinova 1997, Koudinova et al 1999). Moreover, current scientific evidence assigns Aβ with an essential role in the mechanisms of synaptic function, plasticity, learning and memory (discussed below). Until recently, the amyloid hypothesis was the major hypothesis of AD research, however, these scientific facts make it hard to accept the amyloid cascade hypothesis. Over the past decade, the amyloid cascade hypothesis has gradually become a dogma. Yet, the amyloid hypothesis has not successfully attempted to explain the disease pathogenesis through the prism of pathogenetic primacy of amyloid deposition in the brain tissue of affected individuals (c.f. Sobów et al. 2004). However, this hypothesis was the basis for a therapeutic approach tackling brain amyloid by anti-amyloid vaccination or immunotherapy (reviewed in Robinson et al. 2003). Anti-amyloid vaccination, however, was halted at the beginning of 2002 due to severe adverse effects in a number of phase 2 trial participants.

While there is no question on some role for Aβ in AD, the results of the amyloid vaccination trial triggered many scientists' concern as to whether the amyloid hypothesis is a true approach for AD research (referenced in Koudinov 2002, 2003a,b) since amyloid and amyloid precursor may have important physiological functions (Kamenetz et al. 2000, 2003).

ROLE OF Aβ IN MEMORY AND SYNAPTIC FUNCTION: RECENT STATE OF THE ART

Three early electrophysiological studies reported Aβ-mediated increase of long-term potentiation (LTP, an experimental cellular model of learning and memory) in rat dentate gyrus in *in vitro* experiments, indicating Aβ-mediated facilitation of synaptic plasticity. Thus, it was shown (Wu et al. 1995a) that whereas acute treatment of young rat (70-120 days) hippocampal slices with low concentration (100-200 nM) of bath-applied $A\beta_{1\text{-}40}$ did not change basal synaptic transmission, there was an increase in tetanus-induced LTP. Moreover, intracellular (100 nM, *via* the recording pipette) or bath (200 nM) application of $A\beta_{1\text{-}40}$ triggered the slow onset potentiation of NMDA receptor-mediated synaptic currents (Wu et al. 1995b) in hippocampal slices from young rats (70-120 g weight), and did not affect basal AMPA receptor-mediated transmission, resting membrane potential or input resistance of the granule cells. It is very unfortunate that these two articles (Wu et al. 1995a,b) were ignored in latter publications on the neurotoxicity of Aβ (Koudinov and Koudinova 2002b, Walsh et al. 2002). Similar results (of Aβ being a molecule essential for synaptic function) were presented by Schulz, who showed no effect of $A\beta_{1\text{-}42}$ on AMPA currents, and demonstrated an increase of NMDA currents

by the peptide (Schulz 1996). This report proposed that Aβ peptides ($A\beta_{1-42}$, $A\beta_{1-28}$ and $A\beta_{1-40}$) increase the probability of LTP under paradigms that induce little LTP in control slices. Another report (Chen Q.S. et al. 2000) presented data on $A\beta_{1-42}$ and $A\beta_{25-35}$ inhibition of hippocampal LTP at concentrations of 200 nM to 1 μM and no effect at 20 nM. This paper, however, employed a different protocol from earlier reports (Schulz 1996, Wu et al. 1995a,b) (particularly, Sprague-Dawley, not Wistar, rats; 30°C recording temperature; stimulus duration of 0.1 ms delivered through sharpened monopolar tungsten electrodes; the decline of bath-applied peptide just prior to the tetanic stimulation), and missed detailed consideration of $A\beta_{1-40}$.

Several other articles reported on the infusion of Aβ into the rat brain followed by electrophysiological (Cullen et al. 1996, Freir et al. 2001, Itoh et al. 1999, Trubetskaya et al. 2003) or behavioral analysis (Malin et al. 2001, McDonald et al. 1994, Sweeney et al. 1997). The paper of Cullen et al. showed no effect of $A\beta_{1-40}$ (0.4 or 3.5 nmol in 5 μl, equal to the i.v. injection of 5 μl of 0.8 mg/ml (a very high concentration of Aβ, see above) on the ability to induce LTP in hippocampal slices *in vitro*, and the delayed (24 and 48 h after the injection but not at 75 min after injection) reduction in the NMDA receptor-mediated responses recorded *in vivo* (Cullen et al. 1996). It is important to note that another study concluded that "NMDA receptor regulation by amyloid-beta does not account for its inhibition of LTP in rat hippocampus" (Raymond et al. 2003). Another article (Freir et al. 2001) investigated the effect of intra-cerebroventricular injection of Aβ fragments ($A\beta_{15-25}$, $A\beta_{25-35}$ and reverse sequence $A\beta_{35-25}$) on synaptic transmission and LTP in the CA1 region of the hippocampus *in vivo*. This report (Freir et al. 2001) showed an impairment of LTP in a time- (for $A\beta_{25-35}$) and concentration-dependent manner (for $A\beta_{25-35}$ and $A\beta_{35-25}$) but left open the question (as did another recent study by Trubetskaya et al. 2003) what would be the effect of $A\beta_{1-40}$ or $A\beta_{1-42}$ under such experimental conditions. The authors suggested that injection of $A\beta_{1-40}$ at a dose of 300 pmol/day (the volume of injection, however, remained unclear) for 10-11 days impaired hippocampal LTP (Freir et al. 2001). Another earlier article (Itoh et al. 1999) recorded waveforms in *in vitro* hippocampal slices at 25°C (and not at standard 32°C) after the injection of $A\beta_{1-40}$, and expressed LTP as a population spike (PS, not evoked post synaptic potential, EPSP) change *versus* time. Similarly, LTP was expressed as PS change *versus* time in early article on Aβ oligomers (Lambert et al. 1998); this article (Lambert et al. 1998) also missed representative waveforms presentation. Another earlier report showed no evidence of $A\beta_{1-40}$ accumulation or neurotoxicity after the injection of the peptide into rat hippocampus (McDonald et al. 1994) and a recent behavioral study reported an increase of synaptic AβPP with learning capacity in rats (Huber et al. 1997). AβPP was also shown to modulate long-term depression (LTD), another important parameter of neuronal plasticity. Thus, bath application of the soluble AβPP (100 nM, 1 h) adsorbed the ability of rodent hippocampal slices to maintain LTD (referenced and discussed in Koudinov et al. 2001b). Behavioral analyses were characterized by both the absence and the presence of Aβ effect on learning and memory in different behavioral experiments (Malin et al. 2001, McDonald et al. 1994, Sweeney et al. 1997).

Several reports further addressed the puzzling issue of the role of the structural properties of Aβ for neural function. These reports showed that oligomeric (Gong et al. 2003, Lambert et al. 1998, Walsh et al. 2002, Wang et al. 2002) and plaque (Chen G. et al. 2000, Kim et al. 2001, Koudinov et al. 2001b, Stephan et al. 2001) amyloid is capable of impairing synaptic or behavioral plasticity, possibly due to the break of neuronal microcircuitry (Koudinov et al. 2001b). However, these studies of oligomeric Aβ (as well as the latest study by Kayed et al. 2003) and neurotoxicity fail to consider the physiological association of Aβ with lipoproteins that potently arrests peptide toxicity (Cedazo-Minguez et al. 2001, Farhangrazi et al. 1997, Koldamova et al. 2001). This lack of important experimental consideration creates a critical flaw in all studies of Aβ oligomers (Gong et al. 2003, Kayed et al. 2003, Koudinov and Koudinova 2002b, Lambert et al. 1998, Walsh et al. 2002, Wang et al. 2002) and negates the possible pathophysiological relevance of Aβ oligomers (Koudinova 2003, Marchesi 2003).

One other recent investigation suggested age-related impairment of synaptic transmission (but not synaptic plasticity) in transgenic mice that overexpress the human AβPP "Swedish" mutation (Fitzjohn et al. 2001), while the report by Richardson et al. showed that ultrastructural and behavioral changes precede amyloid deposition in a transgenic model of AD (Richardson et al. 2003). The latter study implies a need to critically re-evaluate another dogma, a universal belief that transgenic animals expressing normal or mutated transgene

for AβPP represent a true model for AD type neurodegeneration and also brings into doubt the validity of the amyloid cascade hypothesis (Atwood et al. 2002, Jucker et al. 1992, Marx 1992, Smith et al. 2002a,b, Wirak et al. 1991). Certainly, it begs the quest for other promising approaches to this disease (Alzheimer Research Forum: Current hypotheses 2003).

Based on the above *in vitro* and *in vivo* electrophysiological and behavioral studies of Aβ protein, it is impossible to conclude their relevance to brain physiology or AD. The same is true for several most recent articles aiming to clarify the receptor machinery and signaling cascades involved in Aβ-mediated modulation of synaptic plasticity (Chen et al. 2002, Freir and Herron 2003, Frier et al. 2003, Nakagami and Oda 2002, Vitolo et al. 2002). For this reason in our own recent study (see below), we focused on a different experimental condition (Koudinov and Koudinova 2001a,b, 2002a, 2003a,b). There are, however, two clear-cut conclusions. The first conclusion represents the title of this article: Alzheimer's amyloid-beta (Aβ) is an essential synaptic protein, not neurotoxic junk. The second one is a sad fact that the vast majority of articles relating Aβ as a bad neurotoxic molecule fail (as described by the "Uniform requirements for manuscripts submitted to biomedical journals", available at: http://neurobiology-oflipids.org/submissions/uniformalreq.html) to acknowledge critical studies by others showing an essential role for Aβ in brain neurochemistry and the beneficial effect of the peptide on synaptic plasticity.

AMYLOID-β RESTORES HIPPOCAMPAL LONG TERM POTENTIATION: A CENTRAL ROLE FOR CHOLESTEROL

We recently attempted to dissect out the role for Aβ in synaptic plasticity in brain slices from adult male rat hippocampus under the condition that we characterized previously with regard to cholesterol and phospholipid synthesis (Koudinov and Koudinova 2001a, 2003a). The prolonged maintenance of slices in a test tube for more then twenty hours in our experimental setup preserved synaptic function (e.g., input/output curve (I/O), a basic measure of synaptic function) but abrogated synaptic plasticity (LTP). Aβ protein (1-40), representing the major form of soluble Aβ (Koudinov et al. 1996a, Koudinova et al. 1996a), rescued LTP whereas inhibition of cholesterol synthesis with a statin abolished LTP restoration by the peptide (Fig. 1).

Our observation implies an intriguing perspective that Aβ protein is a functional player in activity-dependent cholesterol neurochemical pathways and confirms an important role for Aβ in synaptic structure-functional plasticity (Kamenetz et al. 2000, 2003, Koudinov and Koudinova 2001a,b, 2003a, Schulz 1996, Wu et al. 1995a,b). The finding also supports our proposed hypothesis that the change in Aβ biochemistry in AD and related disorders is a functional (but not pathologic) compensatory phenomenon aiming to counterbalance impaired cholesterol dynamics and associated neurotransmission and synaptic plasticity (Koudinov and Koudinova 2001a,b, 2003a,b). Such cholesterol-mediated failure of synaptic function and neural degeneration, in our view, represents the cause of the major sporadic form of AD (Koudinov and Koudinova 2001a,b, 2003b).

The above data supports our previous reports that Aβ is a "good" molecule (Kamenetz et al. 2000, 2003, Wu et al. 1995a,b, Schulz 1996) essential for neural/synaptic structure-functional plasticity (rather then synaptotoxicity claimed by amyloid hypothesis and Aβ neurotoxicity proponents (Hardy and Selkoe 2002, Walsh et al. 2002). Such a viewpoint is additionally supported by several studies by others, particularly, by an increase of synaptic AβPP with learning capacity in rats (Huber et al. 1997), by neuronal activity dependent secretion of natural Aβ (Kamenetz et al. 2000, 2003), up-regulating a synaptic vesicle protein transcript by $A\beta_{1\text{-}42}$ (Heese et al. 2001), a transient increase of synaptic Aβ after perforant pathway lesioning (Lazarov et al. 2002), detection of AβPP and its regulatory protein, Fe65, in growth cones and synapses *in vitro* and *in vivo* (Sabo et al. 2003), and the modulation of the AβPP processing by several neurotransmission systems including cholinergic (Isacson and Lin 2000, Hock et al. 2000), glutamatergic (Nitsch et al. 1997) and serotoninergic (Nitsch et al. 1996) systems. Therefore, there is the possibility of a bidirectional modulation between Aβ, AβPP and metabotropic and ionotropic receptor molecules and signaling pathways (Blitzer et al. 2000, Good et al. 1996, Hock et al. 2000, Isacson and Lin 2000, Kar et al. 1996, Nitsch et al. 1996, 1997, for additional discussion see also Koudinov et al. 2001b). In fact, the generation of Aβ is regulated by the phosphoinositide (PI) pathway, which commonly couples to transmitter receptors; and Aβ peptide is also capable of activating the PI pathway in Xenopus oocytes expressing rat brain

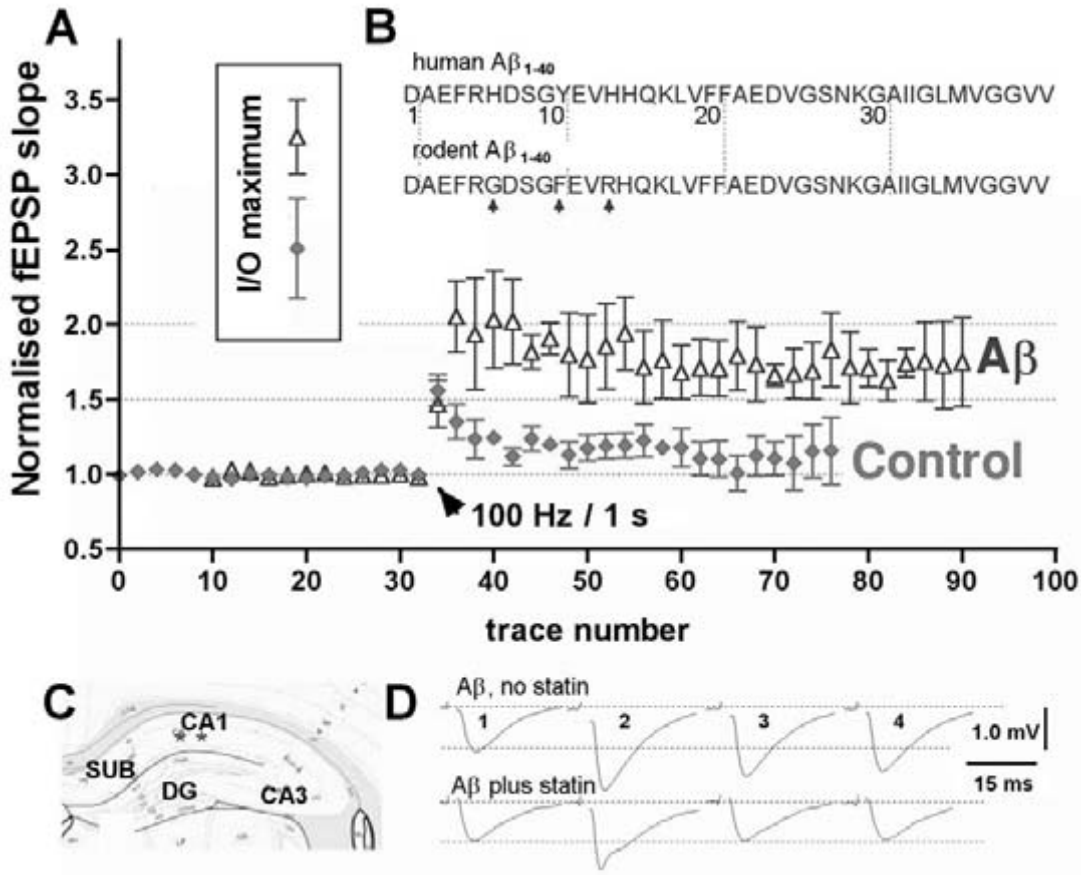

Fig. 1. Effect of Alzheimer's $A\beta_{1\text{-}40}$ on synaptic plasticity in CA1 area of adult rat hippocampus. (A) Field excitatory postsynaptic potentials (fEPSPs) recorded from a single site in stratum radiatum of CA1 under the condition of the prolonged incubation of slices without the peptide $A\beta_{1\text{-}40}$ (control) or in the presence of the peptide (Aβ) are presented as normalized slopes *versus* time to yield LTP charts. Aβ peptide reversed the impairment of the LTP, a characteristic of synaptic plasticity, in slices subjected to 21+ h of maintenance *ex-vivo*, and made it statistically not different ($P>0.05$, nonparametric Mann-Whitney signed rank test, one-tailed) from the slices maintained for 6-8 h only. Inset (I/O maximum) illustrates the maximum values of the input-stimulus/output-response (I/O) curves (indicative of basic synaptic function) that show no statistical differences ($n = 6$, $P>0.05$, one-tailed) between slices maintained for a prolonged time with Aβ or without the peptide. (D) Representative fEPSPs at the bottom right show that statin mevinolin (a cholesterol synthesis inhibitor) abolished LTP restoration by Aβ. The presented waveforms are recorded during the baseline stimulation (1), immediately after the tetanic stimulus (2), as well as three (3) and twenty (4) minutes thereafter. (B) illustrates amino acid sequence differences between rat and used in the study human $A\beta_{1\text{-}40}$. Dots on the schematic hippocampal slice (C) illustrate electrodes positioning. The figure is reproduced by permission from the Neurobiology of Lipid*s* 1: 8 (2003), http://neurobiologyoflipids.org/content/1/8/.

RNA (Blitzer et al. 2000). Aβ also potentiates Ca^{2+}-influx through voltage-sensitive Ca^{2+} channels (Ueda et al. 1997) and was reported to form calcium-permeable channels in lipid vesicles (Lin et al. 2001).

It is very important to notice that Aβ is a structural and functional apolipoprotein constituent of lipoproteins (Koudinov et al. 1994, 1996a,b, 1998b, 2001a, Koudinova et al. 1996b, 2000), and that lipoproteins potently inhibit neural toxicity of Aβ (Cedazo-Minguez et al. 2001, Farhangrazi et al. 1997, Koldamova et al. 2001), a fact unfairly missed in articles serving to validate amyloid cascade hypothesis (Gong et al. 2003, Hardy and Selkoe 2002, Kayed et al. 2003, Koudinov and Koudinova 2002b, Lambert et al. 1998, Walsh et al. 2002). The association of Aβ with lipoproteins is a property of apparent direct relevance to the role of Aβ in the homeostasis of cholesterol and other lipids (Koudinov and Koudinova 2001a) and is also of possible importance for the role of lipoproteins in LTP (Koudinov and Koudinova 2001a, 2002a, Zhuo et al. 2000).

The Aβ-lipoprotein association also serves to maintain Aβ solubility in body fluids (Koudinov et al. 1997, 1998a,b, 1999, 2001a). The evidence-based synaptic function for Aβ and the conceivable lack of Aβ association with lipoproteins in studies of oligomeric Aβ (also called ADDLs) exacerbates the lack of physiological relevance assigned to neurotoxicity by oligomers (Gong et al. 2003, Kayed et al. 2003, Koudinova 2003, Lambert et al. 1998, Marchesi 2003, Walsh et al. 2002, Wang et al. 2002) and leaves the AD field with the question of whether amyloid lowering (by vaccination, secretase modulation or by any other means) could ever be beneficial. This viewpoint is further supported by the "evidence suggesting that loss of endogenous Aβ by the pharmacological inhibition of amyloidogenesis results in a severe reduction in the viability of central neurons. In three different neuronal phenotypes, the pharmacological knock-down of amyloidogenic secretase activity resulted in cell death. This study further supports a key physiological role for the enigmatic amyloid beta peptide" (Plant et al. 2003). Finally, our latest report indicates the possibility of mistaken identity of lipoprotein-bound soluble monomeric apolipoprotein (apo) Aβ as plaque or oligomeric Aβ in contemporary AD research (Koudinova 2003, Koudinova and Koudinov 2003).

CONCLUSIONS

In agreement with the research by others, our data suggest that Aβ improves synaptic plasticity and that this effect may be due to the modulation of neural cholesterol dynamics by the peptide (Koudinov and Koudinova 2001a, 2003a,b). The role for Aβ (as a normal human protein) in mediating essential neurochemical pathways, however, is unlikely limited to cholesterol homeostasis. Other pathways can not be excluded and should be studied further in greater detail. One such candidate is the oxidative stress cascade (Koudinova et al. 2003, Pogocki 2003), also shown to be critical for synaptic function and plasticity (Berezov and Koudinov 2003, Kamsler and Segal 2003, Koudinov and Koudinova 2001c). The slow onset LTP (pharmacologically induced by vitamin E (Xie and Sastry 1993) and Aβ (Schulz 1996, Wu et al. 1995a), but impaired in transgenic mice overexpressing enzyme SOD-1 (Koudinov and Segal 1998) may be attributed to the lipid antioxidant properties modulation by vitamin E or Aβ (Kontush et al. 2001, Koudinova et al. 2003, Xie and Sastry 1993) and dependency of slow LTP component on a unique molecular mechanism.

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