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AMYLOID BETA PROTEIN RESTORES HIPPOCAMPAL LONG TERM POTENTIATION: A CENTRAL ROLE FOR CHOLESTEROL?

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There is no understanding of the role of amyloid beta protein (A β) in brain function and Alzheimer's disease. In the present study we attempted to dissect out the role for A β in the synaptic plasticity in adult rat *ex vivo* hippocampal slices. The prolonged incubation of slices in our experimental setting preserved basic synaptic physiology but abrogated tetanus induced long term potentiation (LTP). Peptide A β 1-40 rescued LTP while cholesterol synthesis inhibition abolished the restorative action of the peptide. Our observation confirms that A β protein is a functional player in cholesterol neurochemical pathways and in synaptic structure-functional plasticity. The finding also supports our proposed hypothesis that the change in A β biochemistry in Alzheimer's disease is a functional phenomenon aiming to compensate impaired cholesterol dynamics and associated neurotransmission and synaptic plasticity failure.

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EPIGRAPH

"The half-century of lipophobia in the United States maybe abating with some return of sanity on the

discussion of health and dietary fat.¹ The youngesy victims of this collective, decades long madness are those infants deprived for one reason or another of breast milk. They are unable to speak for themselves at a time of greatest need for cholesterol during growth, the most critical period of myelination of central and peripheral nervous system, formation of bone and bile, and of every, steroid hormone. Some of the commercial formulas they are fed contain only 1 or 2 mg of cholesterol per 100 g edible portion contrasted with almost 14 mg in breast milk. One can only hope that the confidence in their endogenous ability to synthesize sufficient amounts of cholesterol is not misplaced".²

INTRODUCTION

Nowadays an increasing number of scientific papers implicates cholesterol in Alzheimer's disease (AD).^{3-5WEB+} Directed by the amyloid dogma of AD research these articles discuss an involvement of cholesterol in AD pathogenesis mostly through the modulation of amyloid β protein (A β) manufacturing and deposition. In our recent contribution we proposed an alternative reasoning that cholesterol homeostasis biological misregulation itself has a key role for synaptic plasticity impairment, neuronal degeneration and is the primary cause for several AD hallmarks not limited to brain amyloid.^{5WEB+} We also proposed that the change in A β neurochemistry in the disease represents physiological mechanism aiming to compensate impaired neural cholesterol dynamics and associated neurotransmission and synaptic plasticity failure.³⁻⁵

Our recent study demonstrated that rats fed a cholesterol diet possess impaired hippocampal long-term potentiation (LTP), spatial behavior, Alzheimer's-like brain amyloid and increased neural synthesis of cholesterol and phospholipids.^{5WEB+,6} Acute modulation of cholesterol dynamics (particularly, an increase of cholesterol efflux that models an inability of tissue to redistribute cholesterol and other lipids via lipoprotein (LP) transport) in the hippocampal slices injured both neurotransmission and synaptic plasticity,^{3,7} caused disruption of neurofilament and increase of PFH-like tau phosphorylation (reproduced in several studies, see Refs. 3,5 for citations' details), but preserved the pattern of A β immunofluorescence.³

Except of the above reports,^{3WEB+,5WEB+} there were no other study that would examine interrelation of A β and brain cholesterol turnover with respect to synaptic plasticity, deficit which represents the major Alzheimer's functional abnormality. In the present study we evaluated the effect of A β on hippocampal LTP and attempted to test its dependency on hippocampal cholesterol dynamics (see *Supplement section* below for additional background information).

EXPERIMENTAL

All experimental procedures were previously reported in details.^{3WEB+,7-9} Briefly, brains from adult albino Wistar rats (3-4 months, 300-380g) were rapidly removed and placed into cold (2°C) artificial CSF (ACSF). Transverse hippocampal slices (400 μ) were prepared with a McIlwain tissue slicer within 4 min of an animal decapitation. After standard recreating incubation at room temperature for 1.5 h in ACSF, slices were subjected to pharmacological treatment (for 18-24 hrs) with the human peptide A β 1-40 (0 and 0.33 μ g/ml [83 nM] in ACSF, see Ref. 3) and 0.3 μ M mevinolin,^{7,10,11} followed by washing for 3 min (5x) in ACSF and extracellular field recording of evoked postsynaptic potentials (fEPSP) in stratum radiatum of CA1. Electrophysiological recording was performed as described.^{3,5,8} The tetanic stimulation was delivered at the stimulus intensity that yielded double (compared to baseline responses) EPSP amplitude. The input-stimulus/output-response (I/O) relationship and LTP were expressed as a fEPSP amplitude and slope change versus stimulus intensity and time, respectively. In selected experiments hippocampal slices were subjected to metabolic labeling with [¹⁴C]acetate to evaluate the synthesis of cholesterol and phospholipids.³ The data are presented as mean \pm SEM. Nonparametric Mann-Whitney signed rank test was used for determining significant differences between experimental values. A probability of 0.05 (one-

tailed) or less was accepted as statistically significant.

RESULTS

Prolonged incubation of slices (for 21+ hours) in our experimental condition did not affect basic synaptic physiology (**Fig. 1A**, inset), but adsorbed the ability of slices to induce/maintain LTP in CA1 area of the hippocampus; an initial post-potential level reached 135.2 \pm 20.53 % and fell down to 120 \pm 11.48 % and 113.0 \pm 34.6 % in 3 min and 20 min after the tetanic stimulation (**Fig. 1A**), compared compared to 2.294 \pm 0.051%, 1.635 \pm 0.061 % and 1.614 \pm 0.061% for the slices maintained *in vitro* for 6-8 hrs (n=6 slices, P=0.0011, P=0.007 and P=0.0023, respectively, Ref. 3). The incubation of slices with the peptide A β 1-40, however, resulted in recovery of LTP. After the incubation with A β (83 nM) initial postpotentiation level reached 205.3 \pm 47.43%. At 3 and 20 min after tetanic stimulus the potentiation levels were 190.6 \pm 21.43% and 183.1 \pm 49.44%, respectively (**Fig. 1A**). Slices incubated with A β therefore expressed statistical difference with the slices subjected to 21+ hrs of *in vitro* maintenance without A β (n=6 slices, P=0.019, P=0.0048 and P=0.033, respectively). A β thus reversed the LTP impairment of 21+ hrs slices and made it statistically not different from the slices maintained *in vitro* without A β for 6-8 hrs only (n=6 slices, P=0.1286, P=0.2317 and P=0.3939 for the fEPSP slopes recorded immediately after, in 3 min and in 20 min post-tetanus, respectively). The treatment of slices with A β and mevinolin abolished the restoration of LTP by A β , and reversed fEPSP waveforms back to the condition of the prolonged incubation with no A β (**Fig. 1D**).

In our study we focused on the role of A β 1-40 in synaptic plasticity under the condition characterized previously with regard to cholesterol and phospholipid status.^{3,5} This condition, however, is different from those used in other reports on the role of A β in synaptic function and plasticity (see *Supplement*). Hippocampal slices are characterized by the basal efflux of lipoprotein cholesterol (4.0 \pm 1.23% of the hippocampal cholesterol in 6 hrs, see Ref. 3). This efflux rate in 18 hours could yield the removal of ~12 % hippocampal cholesterol. Such loss of cholesterol in the medium is compatible with the preservation of the basic synaptic physiology but may explain the impairment of LTP in slices^{3,7} subjected to prolonged incubation in the medium in the absence of the external cholesterol donor.¹² On the other hand, peptide A β 1-40 increases cholesterol synthesis (~145% above the control value in 21 hrs) and is capable to enhance the uptake of cholesterol

($132.5 \pm 11.25\%$ above the control in 21 hrs) by the hippocampal slices (see Ref. 3 for experimental details and related discussion). Thus, the restoration of the hippocampal LTP by the peptide A β 1-40 could be caused by replenishment of hippocampal cholesterol to the level equal or exceeding the loss of lipoprotein cholesterol during the prolonged incubation of the slices.³ Additional support for restoration of LTP by A β -mediated biological regulation of the hippocampal cholesterol supply comes from the inhibition of A β effect by mevinolin. Mevinolin is a member of a group of

drugs, called statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes rate-limiting reaction in cholesterol biosynthesis. The concentration of mevinolin used in this study causes 50 % inhibition of HMG-CoA reductase, does not affect nonsterol isoprenoid pathway products (**Scheme 1**), and was reported to inhibit neuronal cholesterol content to near 50%^{7,10,11} Notably, cholesterol synthesis inhibition completely abolished the maintenance and did not significantly affect the induction of the LTP (**Fig. 1**).

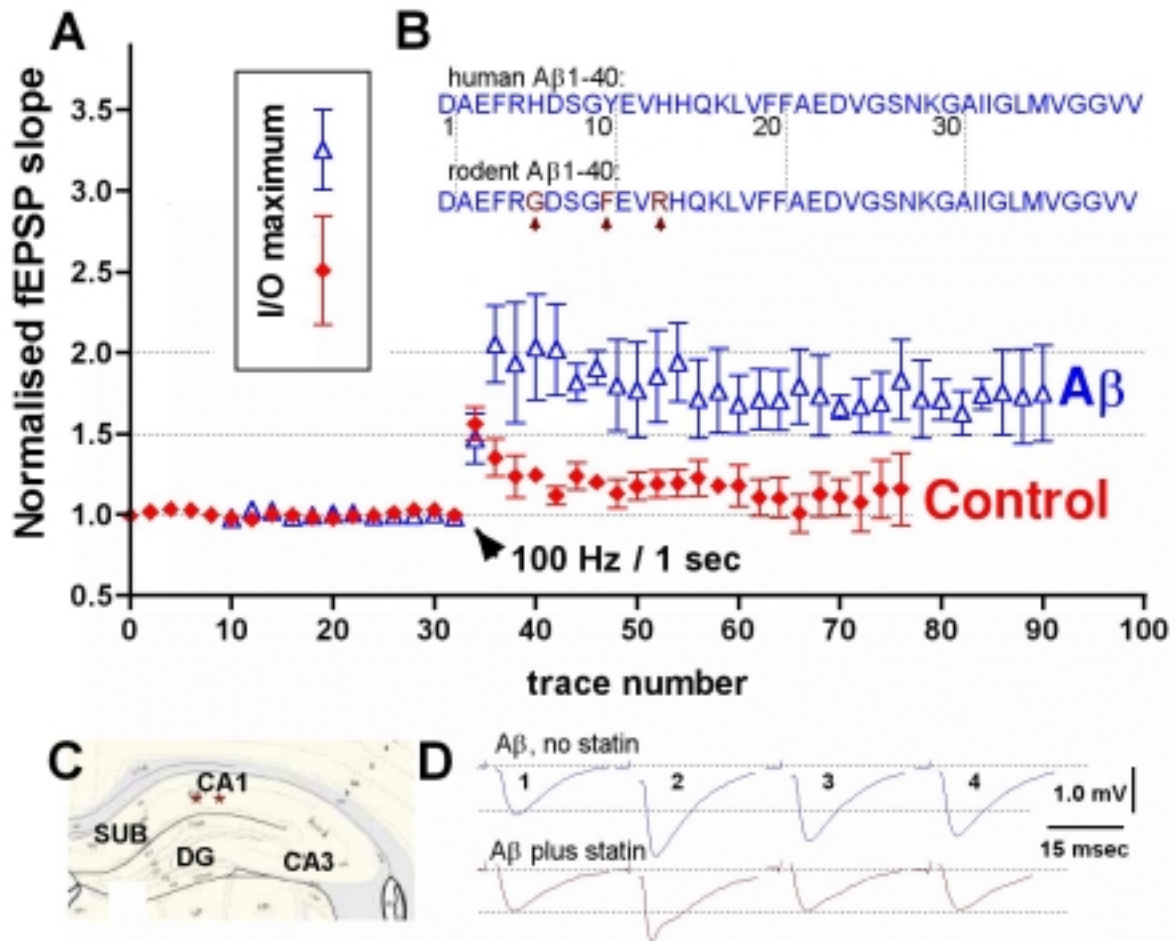


Figure 1. Effect of Alzheimer's A β 1-40 on synaptic plasticity in CA1 area of adult rat hippocampus. A, Field excitatory postsynaptic potentials (fEPSPs) recorded from a single site in stratum radiatum of CA1 under the condition of the prolonged incubation of slices without the peptide A β 1-40 (Control) or in the presence of the peptide (A β) are presented as normalized slopes versus time to yield LTP charts. A β peptide reversed the impairment of the LTP, a characteristic of synaptic plasticity, in slices subjected to 21+ hrs of *in vitro* maintenance, and made it statistically not different from the slices maintained for 6-8 hrs only (see text). Inset (I/O maximum) illustrates the maximum values of the input-stimulus/output-response (I/O) curves (indicative of basic synaptic physiology) that show no statistical differences ($n=6$, $P<0.05$, one-tailed) between slices maintained for a prolonged time with A β or without the peptide. D, Representative fEPSPs at the top right show that statin mevinolin, a cholesterol synthesis inhibitor (see Scheme 1 for details) abolishes restored by A β LTP (see text for discussion details). 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. **Panel B** illustrates amino acid sequence differences between rat and used in the study human A β 1-40. Dots on the schematic hippocampal slice³ (**Panel C**) illustrate electrodes positioning.

DISCUSSION

Amyloid β aids synaptic plasticity by facilitating neural cholesterol dynamics and cholesterol availability. In this report the prolonged maintenance of the adult rat hippocampal slices in a test tube for more than twenty hours preserved synaptic function (input/output characteristics, a basic measure of synaptic function) but abrogated synaptic plasticity (measured as LTP). A β protein of the 1-40 aminoacids' molecule length (representing the major form of soluble A β , a normal human CSF apolipoprotein, see below) rescued LTP while cholesterol synthesis inhibition with a statin reversed the LTP restoration by the peptide.

These results and our past study of the facilitatory role for A β in the hippocampal cholesterol synthesis and the hippocampal cholesterol uptake indicates that A β may function to compensate impaired cholesterol dynamics and associated break of neuronal and neural networks integrity, neurotransmission, synaptic plasticity, learning and memory.^{3,13-15} Such possibility is in accord with the previous data that showed the dependency of neural and synaptic plasticity on the inhibition of cholesterol biosynthesis pathway,⁷ fine tuned neuronal and astrocytic lipoprotein shuttle,^{3,16} its' receptor machinery,^{17,18} and signalling properties.^{19,20} The differential effect of mevlinolin co-incubation with A β on the LTP maintenance, not on the LTP induction (proposed to depend on time demanding cholesterol synthesis and instantly available lipoprotein cholesterol, respectively³) indicates that under this experimental condition lipoprotein uptake in hippocampal slices remained functional, possible due to a facilitatory effect of A β on cholesterol uptake.^{3,21} The stimulation of the neuronal lipoprotein receptors by cholesterol synthesis inhibition (shown for mevlinolin in liver of experimental animals^{22WEB+}) may also contribute to the preservation of the LTP induction after slice incubation with A β and mevlinolin. The above consideration is in accord with the role for cholesterol proper in the synaptic structure-functional plasticity.^{3WEB+}

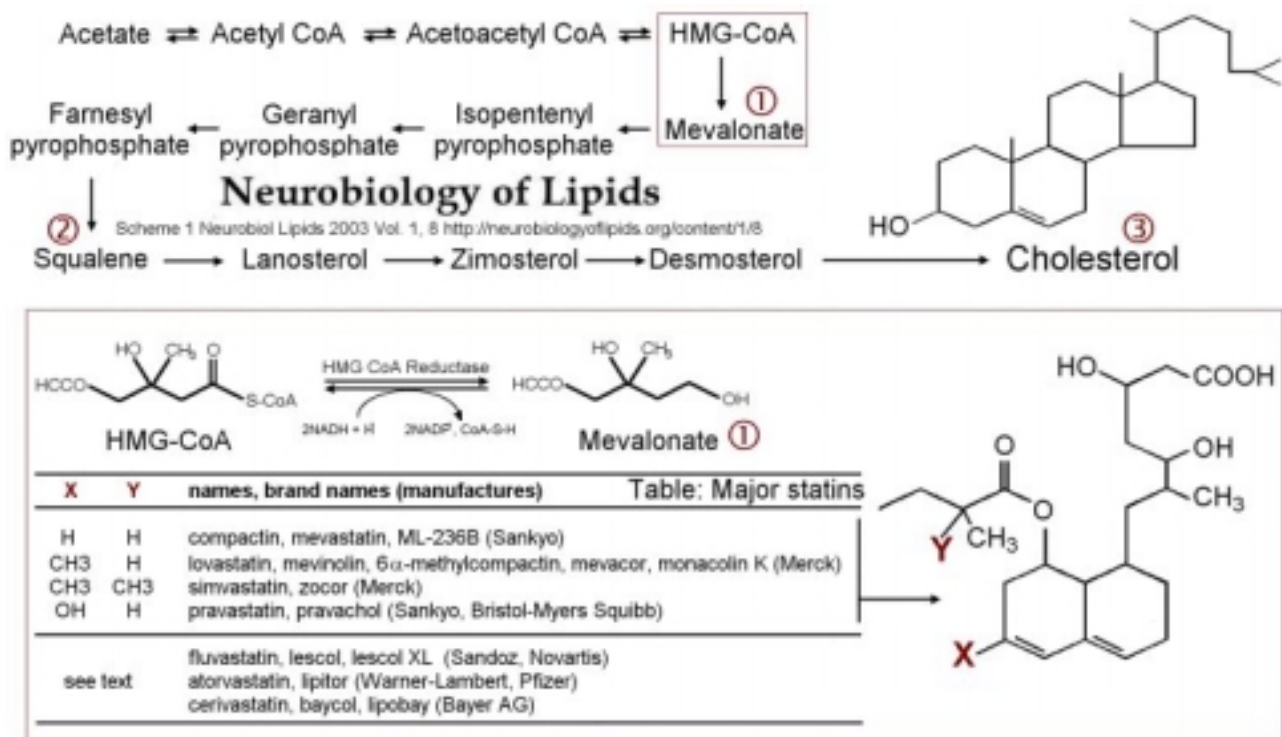
It was previously shown that low dose of A β 1-40 in acute experiment facilitates tetanus-induced LTP²³ and causes the development of slow onset potentiation in the absence of tetanic stimulation.²⁴ Such effect of A β 1-40 may well be similarly due to an increase of A β -mediated neuronal cholesterol synthesis and lipoprotein-receptor facilitated cholesterol uptake.^{3,17,18,23,24}

Function for A β in cholesterol metabolism and membrane dynamics. The data presented here imply functional significance for the relation of the

neurochemistry of A β and cholesterol in synaptic plasticity. It is known that A β modulates neuronal cholesterol esterification,^{25,26} uptake (or influx, see Refs. 3, 21), and efflux.²⁷ These are essential processes that are critical for neural cholesterol intracellular compartmentation and storage, extracellular trafficking, structure-functional membrane dynamics, and lipid raft structure (see Refs. 3, 5 for detailed bibliography). On the other hand, amyloidogenic processing of the amyloid precursor protein (APP) depends on lipid rafts.²⁸ A β modulates membrane biophysical properties, particularly cell membrane fluidity^{29,30WEB+} essential for functioning of a number of receptors critically dependent on fine tuned homeostasis of cholesterol and lipid rafts.³¹⁻³⁴ Most relevant to the current study may well be A β -mediated increase of cholesterol synthesis and cholesterol uptake by *ex vivo* hippocampal slices,³ also reported in PC12 and rat primary neuronal cell cultures and in fetal brain.⁹

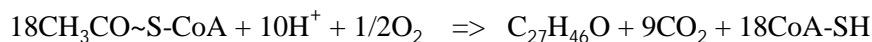
APP and A β represent integrated sensor-effector system for neural cholesterol and membrane dynamics regulation (detailed in Ref. 35).

Function for A β in cholesterol metabolism and recent data on the importance of cholesterol compartmentation for A β generation^{28,36,37} indicate feedback functional relation between cholesterol and A β homeostasis. It is additionally supported by a dependency of APP processing and A β production on membrane lipid rafts, caveolae,^{28,38,39} cholesterol level,⁴⁰ intracellular storage,³⁷ sterol regulatory binding proteins (SREBP) signalling cascade, particularly the dependency of A β on the site 2 processing of SREBP and associated inability of cells to upregulate the expression of several enzymes and proteins involved in cholesterol synthesis and turnover.^{41,42WEB+} APP processing and A β generation also depend on shuttle mechanisms of cholesterol efflux, influx and its' receptor machinery, and intracellular trafficking⁴²⁻⁴⁷ (not to be mistaken with the discussed above separate role for A β in the processes of cholesterol shuttle, see above). The specific intraneuronal routing of A β (see online **Fig. 2** of the original poster presentation that illustrates the intranuclear distribution of exogenously added A β 1-40 in neuron, also see Ref. 9) and other C-terminal products of APP processing to the nucleus⁴⁹ opens the possibility that A β exerts the action on neuronal cholesterol dynamics by intranuclear modulation of SREBP signalling, liver X receptors (LXR) signalling,^{43WEB+} or serving itself a nuclear transcription factor regulating genes encoding enzymes, receptors and (apolipo)proteins involved in cholesterol and other membrane lipids homeostasis. Such complex relation could be of



SCHEME 1. CHOLESTEROL SYNTHESIS PATHWAY AND STATINS.

Cholesterol biosynthesis pathway. Cholesterol biosynthesis can be divided into three major steps: the biosynthesis of mevalonic acid (Step 1), the conversion of mevalonate to squalen (Step 2), and the cyclization of squalen to yield cholesterol (Step 3).¹⁰⁵ It was shown that the major source of mevalonate in the liver and muscles is Acetyl-CoA and leucine, respectively.¹⁰⁵ Both molecules in a number of enzymatic reactions form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). HMG-CoA then is getting reduced to mevalonic acid. At the second step mevalonate undergoes phosphorylation in the presence of ATP yielding the synthesis of several phosphorylated derivatives. Decarboxylation of one of it (Mevalonate-5-pyrophosphate, not shown, these reactions are detailed in Ref. 106) yields Isopentenyl pyrophosphate, an active isopren. It is a widely spread in nature molecule that also participates in the synthesis of a number of biochemicals, including natural rubber, carotenoids, side chains of ubiquinone, vitamins K and E. Isopentenyl pyrophosphate become enzymatically isomerized into Dimethylallyl pyrophosphate.¹⁰⁶ The following condensation of Dimethylallyl pyrophosphate and Isopentenyl pyrophosphate yields Geranyl pyrophosphate, a ten carbon molecule. This reaction is associated with the migration of a double bond and the release of one pyrophosphate. Geranyl pyrophosphate interacts with the new molecule of Isopentenyl pyrophosphate and forms Farnesyl pyrophosphate having 15 carbons in its' molecule. Two molecules of Farnesyl pyrophosphate loose their pyrophosphates and interact head-to-head forming a molecule of Squalen having 30 carbons. The formation of Squalen ends the anaerobic phase of cholesterol biosynthesis. The third step (Step 3) is aerobic reducing cyclization of Squalen. This reaction includes double bond migration and yields Lanosterol. The following reactions yield Zimosterol and Desmosterol, an immediate cholesterol precursor: the reduction of Desmosterol yields Cholesterol. The overall reaction for the pathway is presented below:



HMG CoA reductase reaction and statins. The rate-limiting reaction of the pathway is the synthesis of mevalonate from HMG-CoA. The lower scheme box shows the reaction converting HMG CoA (substrate) to mevalonic acid (product). This reaction is catalyzed by the enzyme HMG-CoA reductase subjected to complex regulatory control, including the feed back inhibition by cholesterol, the pathway product.¹⁰⁷ The inhibition of the HMG-CoA reductase is the target of statins (For a story on statin development see Ref. 108). The image at the bottom right presents the structure of some HMG CoA reductase inhibitors listed in the upper section of the scheme Table. These statins have different substituents at the position X and position Y of the molecule.¹⁰⁸ The chemical structure of fluvastatin, atorvastatin and cerivastatin is available elsewhere.^{108,109}

Statins and brain disorders. Despite the fact that statins are blockbuster drugs^{107,108,110,111} the systemic biological consequences of their prolonged use and their effects on brain lipid chemistry, function, plasticity, and neurodegeneration are not understood. This fact is illustrated by an unfortunate death toll associated with the usage of Bayer's Baycol (Cerivastatin that is removed from the market) due to rhabdomyolysis,^{112,113} by a statin-induced polyneuropathy¹¹⁴ and memory loss,¹¹⁵ and by the lack of consensus on a role of statins in A β biology.¹¹⁶ Statins, however, show promise for Alzheimer's disease prevention and treatment,¹¹⁷⁻¹²¹ and are the subject of patents^{122,123} and Alzheimer's disease clinical trials.¹²⁴ One may wish the understated challenges of statin use¹¹⁰ will get deserved priority by scientists and funding agencies independent of statin manufactures.

major importance in the CNS for normal synaptic function, plasticity (activity-dependent, developmental and under recovery from injury), neurodegeneration, sporadic and familial (fAD) Alzheimer's disease (detailed in Ref. 35).

A matter-of-fact: A β is an essential synaptic protein, NOT neurotoxic junk. Despite a decade long universal publication and grant review bias in favor of the view on A β as solely neurotoxic (this viewpoint is essential to advance non-validated amyloid hypothesis into clinical application^{50,51}) current scientific evidence leaves little doubt that A β serves an essential role at synapse and in synaptic structure-functional plasticity that underlie learning and memory.

Thus it was shown that whereas acute treatment of rat hippocampal slices with low concentrations of bath applied peptide A β 1-40 does not change basal synaptic transmission, there is an increase in tetanus induced LTP.²³ Moreover, A β 1-40 triggered the slow onset long-term potentiation of the NMDA receptor-mediated synaptic currents²⁴ in the hippocampal slices from young rats, but did not affect the basal AMPA receptor-mediated transmission, resting membrane potential or input resistance of the granule cells. Similar results were presented by Schulz, who showed no effect of A β 1-42 on AMPA currents, but demonstrated the increase of NMDA currents by the peptide.⁵² This report proposed that A β peptides (A β 1-42, A β 1-28 and A β 1-40) increase the probability of LTP under the paradigm that induced little LTP in control slices.⁵²

Our present study supports previous data on A β as 'good' molecule^{23,24,52} and further implies an intriguing perspective that A β protein is a functional player in an activity-dependent cholesterol neurochemical pathways and in synaptic structure-functional plasticity. The finding also corroborates our proposed hypothesis that the change of A β biochemistry in Alzheimer's disease and related disorders is a functional (but NOT pathologic) compensatory phenomenon aiming to counterbalance impaired cholesterol dynamics and associated neurotransmission and synaptic plasticity.

A role for A β in neural/synaptic structure-functional plasticity (rather than A β synaptotoxicity claimed by amyloid neurotoxicity proponents⁵⁰) is additionally supported by several studies by others, particularly, by an increase of synaptic APP with learning capacity in rats,⁵³ by neuronal activity dependent secretion of natural A β ,⁵⁴ up-regulating a synaptic vesicle protein transcript by A β 1-42,⁵⁵ a transient increase of synaptic A β after the perforant pathway lesioning,⁵⁶ and the modulation of the APP processing by several neurotransmission systems

including cholin-ergic,^{57,58} glutamatergic⁵⁹ and serotonergic⁶⁰ (in turn shown to depend on membrane cholesterol⁶¹) systems. There is a possibility of a bidirectional modulation between A β , APP and metabotropic and ionotropic receptor molecules and signalling pathways.^{44,62-64} Thus, it was shown that the generation of A β is regulated by the phosphoinositide (PI) pathway, which commonly couples to transmitter receptors; and that A β peptide is capable to activate the PI pathway in *Xenopus* oocytes expressing rat brain RNA.⁶⁴ A β also potentiates Ca²⁺ influx through voltage-sensitive Ca²⁺ channels⁶⁵ and was reported to form calcium-permeable channels in lipid vesicles.^{66WEB+}

It is important to notice that A β is a structure-functional apolipoprotein constituent of lipoproteins,^{3,6-69} and that lipoproteins potently inhibit neural toxicity of A β ,⁷⁰⁻⁷² the fact unfairly missed in articles serving to validate amyloid cascade hypothesis.^{50,73,74} A β association with lipoproteins is a property of apparent direct relevance to the role of A β in the homeostasis of cholesterol and other lipids.⁶⁸ A β -to-lipoprotein association also serves to maintain A β solubility in the body fluids.^{29,75} The evidence-based synaptic function for A β and the conceivable lack of the A β association with lipoproteins in the studies of oligomeric A β (also called ADDLs) may exacerbate the lack of the physiological relevance of the oligomers' neurotoxicity^{73,74,76} and face Alzheimer's field with the question whether amyloid lowering (by vaccination, a secretase modulation or by any other means) could ever be beneficial. This viewpoint is further supported by the "evidence suggesting that loss of endogenous amyloid beta 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".⁷⁷ Finally, our latest report indicates a possibility of mistaken identity of lipid-bound soluble monomeric apoA β as plaque or oligomeric A β in a contemporary Alzheimer's research.^{68,78}

Foreground. Our data suggest that A β improves synaptic plasticity by modulating neural cholesterol dynamics.³⁻⁵ The role for A β (as a normal human protein) in mediating essential neurochemical pathways, however, is unlikely limited to cholesterol homeostasis. The other pathways can not be excluded and should be studied further in greater details. One such candidate is oxidative stress cascade,⁷⁹ also shown to be critical for synaptic function and plasticity.^{80,81WEB+} The slow onset LTP similarly pharmacologically induced by

ROLE OF A β IN MEMORY AND SYNAPTIC FUNCTION: RECENT STATE OF THE ART**Essential role for A β in the mechanisms of synaptic function, plasticity, learning and memory remains to be intriguing and not disproved issue.**

Such status quo illustrates an inability of Alzheimer's neuroscience research community to validate amyloid hypothesis despite of intense research and major fields' research funds allocated to it^{4,83-85} Since anti-amyloid vaccination was halted more than a year ago^{4, 84} the question of whether the amyloid hypothesis is true approach for Alzheimer's disease cure was sounded by many scientists.^{4, 85WEB+} This is especially important because associated with the amyloid dogma competing financial interests and bias apparently retard the development of several other promising approaches.^{4, 84-86} The sad reality became illuminated on March 26, 2003 when *Neuron* (a major neuroscience journal) published a feature electrophysiological study on APP and A β synaptic function.⁵⁴ This article by Kamenetz *et al.* was published near three years after it was first submitted and communicated at the Society for Neuroscience Annual Meeting in 2000.^{54WEB+}

The three early electrophysiological studies reported A β -mediated increase of LTP in rat dentate gyrus in *in vitro* experiments, indicating facilitation of synaptic plasticity by A β . Thus, it was shown²³ that whereas acute treatment of young rat (70-120 days) hippocampal slices with the low concentration (100-200 nM) of bath applied A β 1-40 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 β 1-40 triggered the slow onset potentiation of the NMDA receptor-mediated synaptic currents²⁴ in the hippocampal slices from young rats (70-120 g weight), and did not affect the basal AMPA receptor-mediated transmission, resting membrane potential or input resistance of the granule cells. It is very unfortunate that the authors oversight these two articles^{23,24} in their later publication on the neurotoxicity of A β co-authored by a major proponent of the amyloid cascade hypothesis.⁷³ Similar results (of A β being a beneficial molecule for synaptic function) were presented by Schulz, who showed no effect of A β 1-42 on AMPA currents, and demonstrated the increase of NMDA currents by the peptide.⁵² This report proposed that A β peptides (A β 1-42, A β 1-28 and A β 1-40) increase the probability of LTP under the paradigm that induced little LTP in control slices.⁵²

Another recent report,⁸⁶ presented data on A β 1-42 and A β 25-35 inhibition of hippocampal LTP at the concentration of 200nM to 1 μ M and no effect at 20 nM. This paper, however, employed different from earlier reports^{23,24,52} protocol (particularly, Sprague-Dawley, not Wistar, rats; 30°C recording temperature; stimulus duration of 0.1 msec delivered through sharpened monopolar tungsten electrodes; the decline of bath-applied peptide just prior to the tetanic stimulation), and missed detailed consideration of A β 1-40, also proposed in the article (despite of the lack of experimental data) to inhibit the hippocampal LTP.

Several other articles reported on A β infusion into the rat brain followed by electrophysiological⁸⁷⁻⁹⁰ or behavioral analysis.⁹¹⁻⁹³ The paper of Cullen *et al.* showed no effect of low concentration of A β 1-40 (0.4 or 3.5 nmol in 5 μ l, equal to the I.V. injection of 5 μ l of 0.8 mg/ml solution for 3.5 nmol A β 1-40) on the ability to induce LTP in hippocampal slices *in vitro*, and the delayed (presented 24 and 48 hrs after the injection and not observed 75 min after injection) reduction in the NMDA receptor-mediated responses recorded *in vivo*.⁸⁷ It is important to note that the other study concluded that "NMDA receptor regulation by amyloid-beta does not account for its inhibition of LTP in rat hippocampus".⁹⁴ Another article⁸⁸ investigated the effect of intracerebroventricular injection of A β fragments (A β 15-25, A β 25-35 and reverse sequenced A β 35-25) on synaptic transmission and LTP in the CA1 region of the hippocampus *in vivo*. This report⁸⁸ showed an impairment of LTP in a time- (for A β 25-35) and concentration-dependent manner (for A β 25-35 and A β 35-25) but left open the question (as did another recent study, Ref. 90) what would be the effect of A β 1-40 or A β 1-42 in such experimental condition. The authors suggested that injection of A β 1-40 at a dose of 300 pmol/day (the volume of injection, however, remained unclear) for 10-11 days impaired the hippocampal LTP.⁸⁸ Another earlier article⁸⁹ recorded waveforms in *in vitro* hippocampal slices at 25°C (and not at standard 32°C) after the injection of A β 1-40, and expressed LTP as a population spike (PS, not EPSP) change versus time. Similarly, LTP was expressed as PS change versus time in early article on A β oligomers.⁷⁴ Another earlier report showed no evidence of A β 1-40 accumulation or neurotoxicity after the injection of the peptide into rat hippocampus.⁹¹ Recent behavioral study reported increase of the synaptic β -amyloid precursor protein with learning capacity in rats.⁵³ Behavioral analyses were characterized by both the absence and the presence of A β effect on learning and memory in different behavioral experiments.⁹¹⁻⁹³

Several reports further addressed the puzzling issue of the role of A β structural properties for neural function. These reports showed that oligomeric^{73,74,76} and plaque^{8,95-97} amyloid is capable to impair synaptic or behavioral plasticity, possibly due to breaking the neuronal microcircuitry.⁸ All cited above studies of oligomeric A β (also see Ref. 98), while concluding on A β neurotoxicity, however, miss consideration of the physiological association of A β with lipoproteins, that potentially arrests the peptide toxicity.⁷⁰⁻⁷² Such lack of important experimental consideration creates critical flaw of the A β oligomers studies^{73,74,76} and must warn all of a well possible lack of the pathophysiological relevance of A β oligomers.^{68,98} Another recent study suggested age-related impairment of synaptic transmission (but not synaptic plasticity) in transgenic mice that overexpress human APP possessing "Swedish" mutation.⁹⁹ Such observation, however, unlikely contradicts the cited above four studies on the role of mature amyloid deposits^{8,95-97} due to the experimental differences (particularly, the lack of estimation of A β load at the site of the recording, and employed for recording the stimulus intensity of 20 percent of experimental maximum).

At present it is impossible to unite cited above *in vitro* and *in vivo* electrophysiological and behavioral studies and conclude on the relevance of their experimental conditions to brain physiology and Alzheimer's disease. The same is true for several most recent articles aiming to clarify the receptor machinery and signalling cascades involved in A β -mediated modulation of synaptic plasticity.¹⁰⁰⁻¹⁰⁴ For this reason in this report we focused on a different (from the above listed studies) experimental condition that we previously characterized well with regard to cholesterol and phospholipid metabolism status.^{3,5}

It is also important to note that the majority of articles concluding on A β as bad molecule oversight critical studies by others on an essential role for A β in brain neurochemistry and the peptide beneficial effect on synaptic plasticity.

vitamin E^{82WEB+} and A β ,^{24,52} but impaired in the transgenic mice overexpressing enzyme SOD-1⁸⁰ may be attributed to the lipid antioxidant properties modulation by vitamin E or A β ^{79WEB+,82} and dependency of slow LTP component on a unique molecular mechanism.^{8,80-82}

ACKNOWLEDGEMENT

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