

CHOLESTEROL HOMEOSTASIS FAILURE: A UNIFYING CAUSE OF SYNAPTIC DEGENERATION

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Fine tuning of neural cholesterol (chol) dynamics is essential for synapse function, plasticity, behavior.^{1,2} Significant experimental evidence indicates that cholinergic function, ionotropic and metabotropic receptors, reversible change of amyloid beta (Abeta, A β) chemistry, excessive tau phosphorylation, neural oxidative stress reactions, and other features of neuron degeneration depend on fine tuning of chol homeostasis.¹⁻³ These data suggest that chol homeostasis break is the unifying primary cause of sporadic Alzheimer's (AD), neuromuscular diseases, Niemann-Pick's type C disease and Down syndrome, and formulate why rare cases of familial AD associated with mutations in APP and presenilin (PS) genes, are translated into the disorder via membrane chol sensitivity of APP processing by secretases and A β generation. The reciprocal effect of A β on chol synthesis, cellular uptake, efflux, esterification, and its' relation to the LTP restoration β may represent one of the not

comprehend physiological functions of A β .²⁻⁴ This is because the central event for chol-mediated (or any other type) synapse degeneration is an impairment of neurotransmission and synaptic function/plasticity, which triggers a set of physiological compensatory mechanisms to restore broken function. Primary cause of a disease defines the specificity of a chemical neurotransmission break (ex. dopaminergic system in Parkinson's), and the fine tuning of compensatory mechanisms, yielding the unique pattern of neurodegenerative markers overlap in different diseases. The proposed scenario implies that battling secondary degenerative markers sadly has no ability to effectively cure CNS degeneration.

1 <http://www.fasebj.org/cgi/content/abstract/00-0815fjev1>

2 <http://neurobiologyoflipids.org/content/1/8>

3 <http://neurobiologyoflipids.org/news/news2004.html#wsj160404>

4 <http://www.nencki.gov.pl/pdf/an/vol64/koudin.pdf>

Cholesterol and synaptic plasticity

Slide 1: Experimental system of acute modulation of hippocampal cholesterol. One of the specific aims of our study was to gain basic knowledge on the role of cholesterol in synaptic plasticity. We first used naive albino Wistar rats ex-vivo hippocampal slices for acute modulation of tissue cholesterol dynamics, followed by the study of slices electrophysiology and immunohistochemistry [1, 2].

Slide 2: Experimental design. The experimental design included dissection of rat hippocampus, preparation of thin slices (of about 0.5 mm thickness), slices' maintenance in oxygenated artificial cerebrospinal fluid, incubation of slices with model or natural cholesterol acceptors (that increase cellular cholesterol efflux thus modeling increased dynamics), followed by electrophysiology or immunostaining and immunofluorescent analysis. We also performed analysis of cholesterol efflux summarized below.

Slide 3: Biochemical analysis of cholesterol dynamics in slices. We used HDL3, high-density lipoproteins 3, prepared from normal human cerebrospinal fluid, and methyl- β -cyclodextrine. Both are capable to sequester cholesterol in their hydrophobic core thereby greatly enhancing cholesterol removal from cells and modeling increased cholesterol dynamics. Biochemical analysis of the efflux included labeling of slices with tritiated cholesterol before incubation with cholesterol acceptors. We found that six hours incubation with HDL3 (4 μ g/ml by protein) or methyl- β -cyclodextrine (5 mM) cause significant efflux of cholesterol, roughly 30 % and 70 %, respectively [1]. Cyclodextrine was potent to cause significant efflux of 11 % hippocampal cholesterol also at lower concentration (2.5 mM) and short 20 min incubation time [1]. We also analyzed phospholipid efflux by labeling slices with radiolabeled choline, incorporating mostly into phosphatidylcholine. We found appreciable efflux of 7 % hippocampal phospholipids only during 6 hrs incubation with 5 mM cyclodextrine co-featuring the efflux of 70 % hippocampal cholesterol.

Slide 4: Fluorescent analysis of cholesterol dynamics in slices. Fluorescent analysis of cholesterol in slices was performed after the staining of sections with cholesterol binding compound filipin. The analysis was focused on two hippocampal fields, CA1 and Dentate gyrus. Control sections with no cholesterol efflux promotion had cell bodies stained with filipin. This staining was also present at 20 min efflux with cyclodextrine, but disappeared after six hours of cholesterol efflux. The most illustrative were sections of slices subjected to six hours incubation with 5 mM cyclodextrine. This condition caused the removal of filipin staining of the hippocampal pyramidal and granule cell bodies yielding their appearance as unstained dark strips. The mild cholesterol efflux preserved cell bodies staining but caused no staining of cholesterol in neural cell processes. High magnification zoomed at stratum radiatum of the CA1 showed dark appearance of “no staining pattern” of cholesterol removal in the neurites.

Second part of this work, published earlier in the *FASEB Journal* and as letter in Science magazine, included the analysis of electrophysiological properties of slices as presented below [1, 2].

Slide 5: Essential role for cholesterol in synaptic plasticity. We recorded extracellular field evoked postsynaptic potentials (abbreviated as a EPSP) in the hippocampal CA1 stratum radiatum. We found that slices with increased cholesterol dynamics due to cyclodextrine or HDL3 incubation are impaired in input-output relation, the chart of EPSP size versus stimulus intensity, and a parameter of basic synaptic function.

Slide 6: Experimental slices were also impaired in long-term potentiation (LTP) a long-lasting synaptic enhancement that serve a leading experimental system for the synaptic plasticity that underlie learning and memory.

Slide 7: Cholesterol efflux also increased the magnitude of the paired pulse facilitation (abbreviated as PPF), an efficient test to detect changes within presynaptic terminals, to evaluate the dynamic properties of synaptic transmission and short-term plasticity. These results suggest an essential role for cholesterol in basic synaptic physiology, neurotransmission and in both postsynaptic and presynaptic plasticity mechanisms.

Slide 8: Cholesterol disbalance causes hippocampal neural degeneration. We further tested whether impaired hippocampal cholesterol dynamics causes the disruption of normal neuronal cytoskeleton composed of longitudinally arranged neurofilaments and microtubules. We found that cholesterol depletion causes neurodegenerative fragmentation and teardrop varicose widenings of neurites in all hippocampal subfields and the development of paired helical filaments (PHF) of microtubule-associated protein tau in neurofibrillary tangles (NFT) in the terminal sector of the hippocampal mossy fibers.

Specifically, acute experimental cholesterol dynamics break caused tau immunostaining of pyramidal and granule cells of the CA1 and the Dentate Gyrus. We also observed the removal of tau-1 staining. Tau-1 is a monoclonal antibody to all electrophoretic forms of non-phosphorylated rat tau, so, no staining with tau-1 indicated phosphorylation of tau-1 epitopes. This was confirmed by immunostaining of experimental slices with AT8 monoclonal antibodies that recognize PHF-tau phosphatase-sensitive epitope (containing phosphorylated Ser-202 residue) and do not

recognize normal tau [1, 2]. Cholesterol-dependent PHF-like tau phosphorylation was first reported in neuronal cell cultures by Dr. Michikawa and colleagues [3].

Slide 9. Paired helical filaments, PHF, are abnormal filaments. A decade ago they were proposed by Professor George Perry and colleagues to substitute normal neurofilaments in the process of neurodegeneration [4]. To study whether tau phosphorylation is accompanied by a neurofilament change in our experimental system, we performed staining of slices with anti-neurofilament antibody.

Slide 10. As illustrated on the next slide cholesterol removal with cyclodextrine caused neurodegenerative break of the neurofilament integrity, expressing typical for neurodegeneration neurofilament antibody-positive fragmentations and tea-drop varicose widenings of neural processes in all subfields of the hippocampus.

Cholesterol, other lipids, synaptic plasticity, A β and Alzheimer's

Slide 11: Cholesterol imperfection and amyloid beta protein. We also performed immunostaining of slices with 4G8 monoclonal antibodies that specifically stain amyloid beta (A β) protein, the most wanted molecule in Alzheimer's disease research. Under the condition of acute cholesterol modulation with cyclodextrine we did not observe the change in the pattern of A β immunostaining. The change of A β chemistry was observed, however, under the condition of chronic cholesterol modulation in vivo. This was shown in rabbits by Sparks and colleagues [5], in transgenic mice by Refolo and colleagues [6], and by us in laboratory rats fed a 2% cholesterol diet for a prolonged period of time, 4 months or longer [7, 8]. This is illustrated below.

Slide 12: Chronic modulation of cholesterol causes neurodegeneration features. Cholesterol-fed and control animals were subjected to the analysis of lipid synthesis, study of the LTP, and the histochemical analysis of β -amyloid. We also studied the behavior of these animals that is reported elsewhere [9]. Lipid synthesis was studied by incorporation of [C¹⁴]-acetate into the newly synthesized lipids. Radioactive cholesterol and phospholipids were further separated by the thin-layer chromatography (TLC), and counted for radioactivity. We found that rats fed a 2 %

cholesterol diet have increased synthesis of cholesterol and all tested phospholipids (phosphatidylcholine, PC; phosphatidylethanolamine, PE; phosphatidylserine, PS; phosphatidylinositol, PI) in the hippocampus and cortex.

Electrophysiological analysis (Slide 12, Panel F) revealed an impairment of the LTP in the cholesterol-fed animals. LTP break could be reversed by the reversal of the diet to the regular one for a prolonged period of time. Most significant, we found a spectrum of amyloid deposits in cholesterol-fed animals. We observed typical Alzheimer's like plaque amyloid, non-mature plaque missing the dense central core, and vascular amyloid deposits. It is important to note that acute modulation of cholesterol (see above) did not affect A β but featured synaptic plasticity impairment. This is the reason we believe that the change of A β neurobiochemistry in AD is a secondary compensatory event, not the disease cause. As presented below, there is another reason to think so.

Slide 13: A β is a normal structure-functional constituent of lipoproteins. Amyloid beta protein is not only a pathologic deposit in Alzheimer's brain. It also exists normally as a soluble

protein. Soluble A β is present in body fluids and in the cell conditioned media. A decade ago we were the first to report that soluble Abeta is an apolipoprotein constituent of high density lipoproteins in plasma and cerebrospinal fluid. This was later confirmed in several studies by others.

Slide 14: We also reported that cerebrospinal fluid of Alzheimer's patients differs from normal CSF in the distribution pattern of A β across HDL subspecies, and provided evidence of the lack of A β interaction with other apolipoproteins within normal HDL particles. As shown on this slide Alzheimer's CSF features such interaction of A β with apolipoproteins E and J. Association of A β with lipoprotein lipid and apos is important for maintaining solubility of A β in biological fluids, as it is presented in a different session.

Slides 15-16: Early studies of A β involvement on lipid metabolism. Important implication of A β association with the HDL is a possibility of the protein function in lipid metabolism, a property shown for a number of other apolipoproteins.

Investigating these possibilities we earlier showed that A β decreases lipid synthesis in HepG2 liver cells, and that it also affects cholesterol esterification. Others confirmed inhibitory effect of A β on cholesterol esterification. Cholesterol esterification is of great importance for a so called reverse cholesterol transport, a transport of cholesterol from cells to liver from for excretion. The first step of this process is the efflux of cholesterol from cells. Cholesterol esterification is associated with the HDL particles' interconversion, and may well be linked to the change of A β distribution across HDL subspecies in Alzheimer's CSF samples, that is illustrated on the previous slide.

In the follow up experimentation (see next slide) we showed that A β increases cholesterol and phospholipid synthesis in PC12, primary neuronal cells, and in fetal rat brain, and in adult rat slices.

Slide 17: LTP and A β increase hippocampal lipid synthesis. In a separate experimental series we set to test and confirmed that LTP requires neuronal lipid synthesis [1]. To this end we

metabolically labeled slices with [^{14}C] acetate (a precursor label to trace lipid synthesis) after the LTP induction with a tetanic stimulus. Autoradiography revealed the increase in label incorporation into the hippocampal CA1 area after the induction of LTP in stratum radiatum recording pathway as compared with not-tetanized slices subjected to baseline recording only.

This led us to test lipid synthesis in hippocampal slices after high potassium (K^+)-evoked depolarization, and lipid synthesis modulation by the synthetic analog of amyloid β protein, peptide $\text{A}\beta_{1-40}$ [1]. Over the prolonged incubation with the label slices remained viable and actively synthesized phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and cholesterol. $\text{A}\beta$ treatment increased the synthesis of PC, PE and cholesterol on 33, 67 and 46 % above the control values (100 %), respectively. Additional experimentation showed that $\text{A}\beta$ also enhanced the uptake of [^3H]cholesterol by slices on $\sim 32.5\%$ in 6 hrs above the control value (100 %, no $\text{A}\beta$). In contrast, K^+ -evoked depolarization did not significantly change specified lipid syntheses, suggesting that membrane depolarization, basal

synaptic activity and neurotransmission do not enhance hippocampal lipid synthesis as it occurs after long-lasting synaptic enhancement (LTP).

Amyloid precursor protein and A β protein are integrated sensor-effector system for neural cholesterol and membrane dynamics regulation. Function for A β in cholesterol and other lipid metabolism and the data on the importance of cholesterol compartmentation for A β generation indicate feedback functional relation between cholesterol and A β homeostasis [10, 11]. It is supported by a dependency of amyloid precursor protein (APP) processing by secretases and A β production on membrane lipid rafts, caveolae, LRP, apoE, cholesterol intracellular storage, sterol regulatory binding protein (SREBP) signaling (particularly on the deficiency in site 2 processing of SREBP and associated inability of cells to upregulate enzymes and proteins involved in cholesterol synthesis and turnover). APP processing and A β generation also depend on transit of cholesterol via efflux, intracellular trafficking, uptake and its receptor machinery (10, 11). On the other hand, as shown above, A β itself affects the key steps of cholesterol homeostasis including

cellular uptake, efflux, esterification and synthesis; the latter effect is tissue specific (12, 13). While the above complex relation is of major importance for normal synaptic function, plasticity (activity-dependent, developmental and under recovery from injury), neurodegeneration, and sporadic Alzheimer disease, the functional interaction of APP, A β and cholesterol also explains genetic predisposition to neurodegeneration in rare familial (f) Alzheimer's cases having APP or presenilin (PS) mutations, and in Down syndrome, a trisomy 21 (see below). Please note that PS also depends on cholesterol trafficking and itself affects lipid metabolism [14, 15].

Cholesterol and other neurodegenerative diseases

Slide 18: Cholesterol and neurodegeneration hallmarks. In fact, significant experimental evidence (that we attempted to integrate in our earlier contribution [7, 8]) show that cholesterol may be the primary cause for a number of neurodegeneration features in general, and in AD in particular (Figure 1). These features include, but not limited to, the discussed above change in tau

biology and other cytoskeleton rearrangements, the change in oxidative stress reactions [16, also see Refs. 17, 18], and cholinergic dysfunction [7, 8].

Slide 19: We believe that in early phase of Alzheimer's onset these changes serve important compensatory function. This mean that when due to cholesterol failure synaptic machinery breaks, tau, oxidative reactions and β -amyloid may serve to adapt the brain and help to restore the function. Tau phosphorylation may help re-organize cytoskeleton. Oxidative reactions affect membrane lipid peroxidation that modulates synaptic membrane fluidity, critical for receptor function. As reported elsewhere [16], amyloid beta may serve to modulate oxidative cascade reactions, because $A\beta$ normally serves as antioxidant. We showed that $A\beta$ can also modulate lipid synthesis, cholesterol and phospholipids in particular, and thus help to restore neural dynamics of these pivotal lipid membrane components.

Overlap of neurodegeneration hallmarks across the spectrum of neurodegenerative diseases.

It is important to realize that different neurodegenerative diseases express significant overlap in major markers (Slide 19). Some of these features are also present normally during specific period

of ontogenesis, further implying that what we call “pathogenesis markers” are in fact tested by nature developmental or compensatory mechanisms. This means that fighting the conventional disease features, A β and tau for example, will not benefit patients as underlying primary cause will not be cured. But what is a primary neurodegeneration cause?

What is the primary cause for neurodegeneration? Is there a relevance of cholesterol mediated neurodegeneration to different neurodegenerative diseases? If so is there neurodegeneration specificity? We do think so. We believe that cholesterol dynamics failure may be a primary pathogenic cause in a number of diseases, such as Alzheimer’s, Down syndrome, neuromuscular junction (NMJ) disorders, and of course Niemann-Pick’s type C disease. On the other hand other diseases may have another primary pathological break (ex. the break of the forebrain dopamine system in Parkinson’s disease). Even in this case the brain may operate its’ standard set of compensatory mechanisms, causing the overlap of morphologic changes, and explaining the unity of markers across the spectrum of neurodegenerative disorders (Figure 1) [19, 20, 21].

Slide 20: Cholesterol and Alzheimer's disease. For cholesterol and AD we recommend to see *Neurobiology of Lipids*, <http://neurobiologyoflipids.org> . This open access scholar journal established in 2002 hosts several publications on the subject, including abstracts and proceedings articles links for the Society for Neuroscience Annual Meeting 2002, 2003 and 2004, and 2002 Frankfurt, Germany symposium on cholesterol and Alzheimer's disease [22].

Slide 21: Cholesterol and Down syndrome. Down syndrome patients are characterized by reduced cholesterol esterification in plasma [23]. They also have specific pattern of the liver sterol regulatory element binding protein (SREBP) activation, and sterol-independent maturation of SREBP. Down syndrome is also characterized by high circulating and tissue cholesterol levels in utero [24].

Slide 22: Neuromuscular disease, A β /APP metabolism and cholesterol. Further investigation is warranted to elucidate the normal role for amyloid β protein at synapse and neuromuscular junctions (NMJ). Two basic observations include the study published a decade ago [25]. This was the first demonstration of APP and A β concentration postsynaptically at human neuro-muscular

junctions, and let authors to conclude that “APP may have a role in normal junction biology and possibly in some diseases affecting NMJs”. Another study later showed that APP homolog in *Drosophila* (APPL) promotes synapse differentiation at the neuromuscular junction [26], leading the authors to propose a model “by which APPL, in conjunction with activity-dependent mechanisms, regulates synaptic structure and number”. Few years later this pivotal knowledge, changing the neuroscience research community view on A β as solely neurotoxic, was extended with a data obtained for the CNS synapses. The latter study showed activity dependent secretion of A β and proposed roles for A β in synaptic transmission; it was first reported at the Society for Neuroscience Annual Meeting in 2000, and then published in *Neuron* in 2003 [27, 28].

Slide 23: A β , cholesterol and synaptic plasticity: a functional triangle. In our own recent study peptide A β 1-40 rescued synaptic plasticity, while cholesterol synthesis inhibition with mevinolin (a member of a group of drugs inhibiting rate-limiting reaction of cholesterol biosynthesis, HMG-CoA reductase inhibitors, also called statins) abolished the restorative action of the A β peptide.

This observation confirms that A β protein is a functional player in synaptic structure-functional plasticity on one hand, and in cholesterol neurochemical pathways on the other [11].

The change of A β biology and PHF tau phosphorylation are characteristic features of inclusion-body myositis (IBM) [29]. Furthermore, A β accumulation in cerebral vessels and plaques may be much more general neural degeneration phenomenon than previously thought, as it occurs frequently not only in AD, but also in Parkinson's disease (PD), Diffuse Lewy body disease (DLBD), progressive supranuclear palsy (PSP) but not multiple systems atrophy (MSA) or amyotrophic lateral sclerosis (ALS) [30]. This study, however, reports lacking cognitive impairment unusual ALS case marked by extensive cerebral A β deposition in small and medium-size vessels, capillaries, and perivascular plaques in the cerebral cortex, and in most leptomeningeal vessels. The author's conclusion is: "the lack of cognitive impairment in the case presented argues against the idea that extensive amyloid β deposition in the brain causes dementia".

Slide 24: Cholesterol, lipoprotein receptors and Inclusion-body myositis (IBM). Finally, most recent study showed an abnormal accumulation of lipoprotein receptors (including LDL-R receptor, VLDL-R receptor, and lipoprotein related protein, LRP) and cholesterol in vacuolated muscle fibers in inclusion-body myositis [29]. In “all myopathies, a subset of regenerating and necrotizing muscle fibers had prominent diffuse accumulation of both LDL-R and cholesterol” [29]. Lipoprotein receptors govern cellular uptake of cholesterol in its receptor-mediated transport [31]. What is their role at in neurodegenerative diseases and how it is related to cholesterol and synapse normal dynamics and pathological failure remains to be investigated. The detection of lipoprotein receptors at normal NMJ postsynaptically and their abundance in the hippocampus [detailed in Ref. 1] suggests their physiological role for neurotransmission in both peripheral and central nervous system. Explaining our own data (see section “Essential role for cholesterol in synaptic plasticity” above) and integrating them with important studies by others [32, 33] we proposed in 2001 that lipoprotein receptor-mediated cholesterol redistribution and synthesis could be adaptive complementary processes important at early and late stages of the activity-dependent synaptic structure-function plasticity that underlie learning and memory [1].

Slide 25: Apolipoprotein E, cholesterol and neuromuscular diseases. Apolipoprotein (apo) E is known as a major genetic Alzheimer's risk factor [34]. Less appreciated in neurology is the central role for apoE in cholesterol metabolism, as it serves as a major cholesterol transport apolipoprotein. ApoE involvement in AD may be well mediated by apoE role in cholesterol dynamics [35]. Recent review on the subject summarized that apoE may be important in neuromuscular disease in the same way as in Alzheimer's, $\epsilon 4$ allele serving a bad allele, and $\epsilon 2$ being a protective one "against developing certain neuromuscular diseases, including the amyotrophic lateral sclerosis (ALS)/parkinsonism/dementia complex of Guam. ...This allele is [also] associated with a better prognosis in neuromuscular diseases such as motor neuron disease. The effect of various APOE alleles on neuromuscular diseases therefore parallels their influence on central nervous system diseases", the authors conclude [36]. ApoE $\epsilon 4$ homozygosity may also accelerate tau NFT formation and A β deposition in Niemann-Pick type C disease [37].

Niemann-Pick type C disease, cholesterol and neurodegeneration: Niemann-Pick disease type C (NPC) "is an inherited neurodegenerative disorder associated with intracellular cholesterol and

glycolipid trafficking defects. Two separate genes, NPC1 and NPC2, have been linked to NP-C. NPC1 encodes a polytopic membrane-bound protein with a putative sterol-sensing domain. NPC2 has been recently identified as epididymal secretory glycoprotein 1. The NPC1 protein functions in the vesicular redistribution of endocytosed lysosomal cargo” [38], and is a key component in the intracellular distribution of cholesterol obtained from lipoproteins by the endocytic pathway. A mouse model of Niemann-Pick type C disease “exhibits neuropathology similar to the human condition. There is an age-related neurodegeneration in several brain regions and a lack of myelin in the corpus callosum in these mice [39].

One of the explanations “suggest that a functional disturbance in NPC1 could disrupt vesicular transport of cholesterol, glycolipids and possibly other endocytic cargo in glia, which is critical for maintaining the integrity of neurons [38, 39]. The view of NPC neurodegeneration as a pathology of neuronal cholesterol proper was also suggested [40]. “Using filipin fluorometry of neuronal cells in tissue slices, [authors] found massive accumulation of cholesterol in neurons in four out of five human NPC cases. Neurofibrillary tangles composed of aggregates of the otherwise highly

soluble protein tau were present in three Niemann-Pick type C cases and were also immunologically identical to those associated with Alzheimer's disease” [40].

Specificity of cholesterol-mediated neurodegeneration

Slide 26: Cholesterol, neurodegeneration and neurotransmission chemical specificity.

Another important question is: what is the specific mechanism of cholesterol-mediated synaptic function break? Recent and emerging evidence shows that cholesterol affects the pharmacology of the several chemical neurotransmitters, receptor and transporter systems, including cholinergic [41-43], GABAergic [44-46], 5-HT_{1A}/serotonin [47, 48], inhibitory glycine [49] and excitatory amino acid systems [50]. Important latest work on this subject was presented at the Society for Neuroscience 33rd Annual Meeting (November 8-12, 2003, New Orleans, LA), is freely available

at the neurobiology of lipids Neuroscience 2003 neurobiology of lipids sessions' collection (<http://neurobiologyoflipids.org/content/2/3>), and awaits full text publication [48-50].

Cholesterol and the Nicotinic Acetylcholine Receptors (nAChR): Perhaps, the most advanced data are available for the Nicotinic Acetylcholine Receptors (nAChR). The isolated nAChRs express high affinity for cholesterol. Cholesterol is also required for functional insertion of nAChRs into artificial membranes: “only after nAChRs are inserted into the postsynaptic membrane and charged with cholesterol do they become fully active” [41-43]. There are several proposed mechanisms [41]; the details remain to be investigated.

References

All citations at length of this article are available online as a part of *Neurobiology of Lipids* editor's choice full text proceedings article, <http://neurobiologyoflipids.org/content/3/7>

Conclusion

Slide 27: In conclusion this slide itemizes the message to remember:

1. Cholesterol itself plays essential role in the mechanisms of synaptic function, plasticity and neurodegeneration.
2. Central neurodegeneration features in a number of degenerative diseases of the nervous system represent functional consequences of neural cholesterol biological misregulation.

The above *i*) explains the overlap of neurodegenerative hallmarks across the spectrum of neurodegenerative diseases, and *ii*) suggest that cholesterol homeostasis break is the unifying primary cause of sporadic and familial Alzheimer's disease, neuromuscular diseases, Niemann-Pick's type C disease and Down syndrome.