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A LINK BETWEEN CHOLESTEROL, CNS, SYNAPSE AND BRAIN DISEASES: IS THERE A NEED FOR A REINVENTION?

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Since 1987 we know that "apolipoprotein E-containing lipoproteins may function to redistribute lipid and regulate cholesterol homeostasis within the brain". In 1993 we learned about the importance of "cholesterol synthesis and lipoprotein reuptake during synaptic remodeling". Over the past decade this knowledge was amassed (thanks to the pivotal contribution by many scientists) and elucidated the role for the failure of cholesterol homeostasis proper in neuronal degeneration. Still many questions remain. However, the statement that "a breakdown of cholesterol homeostasis may also play a role in neurodegenerative processes that have not been associated with this lipid so far" seems outdated.

One of the key points and discussion matters of our FASEB J article published in June 2001¹ is the statement that in "the CNS, either the apoE-containing lipoproteins secreted by the astrocytes² or CSF-HDL-like particles may function as acceptors^{3,4} and vehicles destined cholesterol to the sites of active plasma membrane rearrangements during the growth of new dendritic processes, accompanying synaptic activity and LTP",^{5,6} and that "by recycling cholesterol via lipoproteins and their receptors, the CNS would have immediate access to the existing brain cholesterol pool for membrane remodeling."

We based our research on several prior pioneering publications and were happy that our results support and are supported by "recent reports that showed that LRP deficit (caused by a receptor-associated protein RAP, an antagonist for ligand interactions with LRP) impairs hippocampal LTP⁷ possible via an NMDA receptor,⁸ and that apoE and LDL-receptor knockout mice are impaired behaviorally."⁹

We highlighted that "lipoprotein-mediated cholesterol redistribution and synthesis could be adaptive complementary processes, important at early and late stages of LTP for neuronal activity-dependent structural plasticity of dendritic spines, believed to be the site of memory formation". Based on our experimental data and previous research by others we concluded on the "importance of neuronal cholesterol redistribution and synthesis for synaptic plasticity and neurodegeneration".

We did not call the above our invention as it was grounded and implied by a pivotal research of many scientists. In addition to the above citations of the FASEB J article²⁻⁹ we enjoyed the research by several other research group, including the study of the role of apolipoproteins for recycling of membrane lipids for use by sprouting neuron fibers to promote neurite extension or in long-term plasticity changes following injury (Refs.10, 11; also see Ref.12); that "apo E is important for AMPA receptor regulation and LTP expression in the hippocampal formation";¹³ "that apoE and the LDL receptor are involved in maintaining the [synaptic membrane] transbilayer distribution of cholesterol";¹⁴ and "that projecting basal forebrain cholinergic neurons... are markedly dependent on

apoE and that similar mechanisms mediate the in vivo and in vitro effects of apoE deficiency on cholinergic function".¹⁵

I therefore was surprised to learn of the reinvention of a role for cholesterol in synapse formation, neural plasticity, and neurodegeneration in recent hypothesis and review articles.^{16,17,18}

Thus, January 2003 *Bioessays* hypothesis "proposes a new type of neuron–glia interaction in the CNS" and states that "neurons import cholesterol from astrocytes via lipoproteins. The cholesterol shuttle may be restricted to compartments distant from the soma including synapses and may be regulated by electrical activity." The article names the above a 'shuttle hypothesis', that further "states that, after differentiation of astrocytes, neurons reduce their cholesterol synthesis and rely constitutively on cholesterol delivery by astrocytes via lipoproteins".¹⁶

There are several problems that dampen the overall impression of the *Bioessays* article despite of the itemization of legitimate questions that neurobiology of cholesterol has to address.

First, the presented proposition is not new. A decade ago we learned about "cholesterol synthesis and lipoprotein reuptake during synaptic remodeling in hippocampus in adult rats".¹⁹ Furthermore, since 1987 we know that "apolipoprotein E-containing lipoproteins may function to redistribute lipid and regulate cholesterol homeostasis within the brain".² The key introductory note of our FASEB J article published near two years ago is that "lipoprotein-mediated transport is assigned an important function in ferrying cholesterol from one cell to another and delivering lipids to the neurites and their growth cones during neuronal membrane biosynthesis for regeneration, synaptic remodeling¹⁹ and synaptic vesicles biogenesis."²⁰ This idea was articulated and experimentally tested in one or another way in the cited above contributions by others (Refs.2-15, 19, 20; also see Table 1).

All these contributions^{2-15,19}, however, are missed in the *Bioessays* 'hypothesis' article. The citation for our own study¹ is not complete. Ignored is our usage of the normal human CSF high density lipoproteins, a natural cholesterol acceptor, mild modeling the inability of neural cells to redistribute cholesterol from one cell to another via lipoprotein transport in the hippocampal slices, followed by the study of the electrophysiological properties of the slices. The feeling is that presented is just that part of experimentation by others that fits the 'hypothesis'.

Similarly problematic is a statement in another review article published a month ago in the *BBA*.¹⁷ It says that "notably, a breakdown of cholesterol

homeostasis may also play a role in neurodegenerative processes that have not been associated with this lipid so far".¹⁷ For the viewpoint by others please see live discussion on 'Cholesterol and Alzheimer's disease' held November 19, 2002 at Alzheimer Forum.²¹

Second, there is a conclusion-style statement not supported by the data. Thus, the abstract of the *Bioessays* article says: "Recent studies on primary cultures of highly purified neurons from the rodent central nervous system (CNS) suggest that, during development, neurons reduce or even abandon synthesis to save energy...". The article text further says that "future studies will show whether cholesterol synthesis and energy metabolism are coupled" and that "future studies need to address ... the question whether the neuronal cholesterol metabolism changes during development". There is a Science article by the same team of researchers that oppositely states in the abstract that "CNS neurons produce enough cholesterol to survive and grow...".²²

This Science article extends "previous reports [that^{23,24}] showed that a glia-derived factor strongly promotes synapse development in cultures of purified CNS neurons... [and] identifies this factor as cholesterol complexed to apolipoprotein E-containing lipoproteins." I appreciate these data and welcome the discussion focus of the Science article. I, however, was similarly puzzled by the omission of the key contributions by others, also missed in an accompanying Science perspective.²⁵ Our correspondence on the latter matter yielded our letter in Science²⁶ as a result of Science offer "to run a version of [our] original dEBate submission in the Letters section, which is the preferred place to address such "oversight" issues".

CONCLUSION

In summary, I believe that we have to build a progress on an integration of the contribution by others with what our studies draw answers for. It is very important that every original research report become noticed and properly acknowledged. This is what "Uniform requirements for manuscript submitted for biomedical journals" requires every prospective author to observe, and a journal to safeguard.²⁷ This is what I wish to see in my research field of the neurobiology of lipids.

COMPETING INTEREST STATEMENT

I do not have any competing financial interest. I serve as founding and managing editor of the *Neurobiology of Lipids*. The viewpoint presented in this correspondence article is my personal view. It does not represent the viewpoint of the journal or its' editorial board members.

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TABLE 1. Key notes of the abstracts of the cited articles.

Boyles JK, Pitas RE, Wilson ER, Mahley RW, Taylor JM. (1987)²:

"In the present work, primary cultures of rat brain astrocytes were used to study apolipoprotein E synthesis, secretion, and metabolism in vitro. ...Apolipoprotein E-containing lipoproteins may function to redistribute lipid and regulate cholesterol homeostasis within the brain."

Blanchette-Mackie EJ, Dwyer NK, Amende LM, Kruth HS, Butler JD, Sokol J, Comly ME, Vanier MT, August JT, Brady RO, et al. (1988)²⁸:

"These findings indicate that components of the Golgi complex play a role in the intracellular translocation of exogenously derived cholesterol and that disruptions of the cholesterol transport pathway at the Golgi may, in part, be responsible for the deficiency in cholesterol utilization in type-C Niemann-Pick fibroblasts."

Poirier J, Baccichet A, Dea D, Gauthier S. (1993)¹⁹:

"Apolipoprotein E is synthesized and secreted by astrocytes in the hippocampus following lesions of the entorhinal cortex... The present findings suggest that non-esterified cholesterol released during terminal breakdown is esterified, transported via the apolipoprotein E transport system to neurons undergoing reinnervation, and take-up through the low-density lipoprotein receptor pathway where it is presumably used as a precursor molecule for the synthesis of new synapses and terminals."

Igbavboa U, Avdulov NA, Chochina SV, Wood WG. (1997)¹⁴:

"This study demonstrates for the first time that synaptic plasma membrane lipid structure is altered in mice deficient in apoE or the LDL receptor. Although the mechanism that maintains the asymmetric distribution of cholesterol in plasma membranes is not well understood, data of the present experiments indicate that both apoE and the LDL receptor are involved in maintaining the transbilayer distribution of cholesterol."

Kleinfeld O, Diebler MF, Chapman S, Oron L, Michaelson DM. (1998)¹⁵:

"These in vitro observations are in accordance with the in vivo findings and suggest that projecting basal forebrain cholinergic neurons, but not cholinergic interneurons, are markedly dependent on apoE and that similar mechanisms mediate the in vivo and in vitro effects of apoE deficiency on cholinergic function."

Rebeck GW, Alonzo NC, Berezovska O, Harr SD, Knowles RB, Growdon JH, Hyman BT, Mendez AJ. (1998)³:

"These data support a model of CSF lipoproteins acting to remove lipids from degenerating cells and delivering lipids to cells for new membrane synthesis or storage."

Teter B, Harris-White ME, Frautschy SA, Cole GM. (1999)¹⁰:

"[Neuronal] Sprouting may be stimulated by estrogen through its up-regulation of apolipoprotein E expression leading to increased recycling of membrane lipids for use by sprouting neurons."

Zhuo M, Holtzman DM, Li Y, DeMaro J, Jacquin M, Bu G. (2000)⁷:

"Here we demonstrate that ... receptor LRP is abundantly expressed in hippocampal neurons and participates in hippocampal LTP"

Posse De Chaves EI, Vance DE, Campenot RB, Kiss RS, Vance JE. (2000)²⁹:

"Inhibition of cholesterol biosynthesis increased LDLR expression in cell bodies/proximal axons but not distal axons. LR11 (SorLA) was restricted to cell bodies/proximal axons and was undetectable in distal axons. Neither the LDL receptor-related protein nor the HDL receptor, SR-B1, was detected in sympathetic neurons. These studies demonstrate for the first time that lipids are taken up from lipoproteins by sympathetic neurons for use in axonal regeneration."

Qiu Z, Hyman BT, Strickland DK, Rebeck GW. (2000)⁸:

"There is increasing evidence that the low-density lipoprotein receptor-related protein (LRP) can function as a signaling link in the central nervous system. To investigate the pathophysiological role of LRP in the central nervous system, we examined the effects of activated alpha(2)-macroglobulin (alpha2M), a ligand of LRP, on intracellular calcium signaling in cultured rat hippocampal neurons."*

Champagne D, Rochford J, Poirier J. (2000)⁹:

"These findings suggest that, in contrast to what has been proposed in the past, apoEKO mice appear not to be impaired in spatial memory per se but are deficient in a procedural component of the Morris water maze."

Koudinov AR, Koudinova NV. (2001)¹:

"Our results indicate importance of neuronal cholesterol redistribution and synthesis for synaptic plasticity and neurodegeneration"

White F, Nicoll JA, Horsburgh K. (2001)¹¹:

"Apolipoproteins are primarily involved in the transport of lipid and cholesterol within the central nervous system (CNS) and are thought to play a role in synaptic remodeling, repair, and regeneration after brain injury... The results indicate that apoE and apoJ are upregulated after injury and parallel clearance of cholesterol and lipid debris from the site of injury. This coordinated alteration in apolipoproteins may redistribute lipid material to sprouting fibers to promote neurite extension and may play an important role in long-term plasticity changes following injury."

Valastro B, Ghribi O, Poirier J, Krzywkowski P, Massicotte G. (2001)¹³:

"These results confirm that apoE is important for AMPA receptor regulation and LTP expression in the hippocampal formation. However, the presence of LTP in aged apoE-deficient animals, together with apparent recovery of the PS action on AMPA receptors, suggests that aged apoE-knockout mice possess compensatory mechanisms that reduce biochemical and electrophysiological alterations of glutamatergic neurons."