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Dedicated to Rita Levi-Montalcini

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DANCE **ROUND**

WE DANCE ROUND *IN A RING AND SUPPOSE, BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.*
ROBERTFROST

NEUROLIPIDOLOGY: INTERACTIONS OF NERVES, NEUROTROPHIC FACTORS, ANDLIPIDS

George N. Chaldakov and Luigi Aloe
Division of Electron Microscopy, Medical University, Varna, Bulgaria and Institute ofNeurobiology, CNR, Rome, Italy

Here we highlight current data of the involvement of cholesterol, lipoproteins and lipoprotein receptors in the neuronal development and of neurotrophic factors in the lipid and glucose metabolism. We term these interactions neuro-lipidology. And argue that in addition to its implication in neurodegenerative diseases such as Alzheimer's disease (1), neurolipidology may have wide-ranging potential within a variety of nonneuronal fields, including cardiovascular disease, particularly, atherosclerosis and related disorders.

Emerging evidence shows that neurotrophic factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), leukemia inhibitory factor (LIF), and hepatocyte growth factor are involved in the process of atherogenesis (2, this *volume of Biomedical Reviews).* Because altered plasma concentrations of low density lipoprotein (LDL), very low density lipoprotein (VLDL), and high density lipoprotein (HDL) are among the principle players in the process of atherogenesis, they have been considered by many authors to act mainly on various cells of the artery wall. However, it appears to be much more than that. Indeed, it is known that LDL receptors (LDLR) can bind not only lipoproteins but also other ligands, and thereby involved in processes not solely related to lipoprotein internalization and metabolism. More recently, the neuronal development becomes one remarkable example of that. Likewise, in addition to their effects on the lipid and glucose metabolism of neuronal cells, as first demon-strated for NGF by Levi-Montalcini, neurotrophic factors may also exert such eff ects on nonneuronal cells, including adipocytes, hepatocytes, and pancreatic beta cells.

CHOLESTEROL, LIPOPROTEINS AND LIPOPROTEIN RECEPTORS AMD NEURONAL DEVELOPMENT

Although cholesterol has long been known to be an essential component of plasma membrane, recent studies have suggested that cholesterol plays an essential role during the development of nervous system (3). Likewise, accumulating evidence suggests that membrane cholesterol and sphin-golipids cluster to form functional rafts that move within the fluid bilayer and influence receptor-mediated signal trans-duction and membrane trafficking (4,5).

Since first demonstrated by Brown and Goldstein, the importance of the LDLR in the regulation of cholesterol homeostasis has been studied intensively by virtue of its malfunction being causally related to atherosclerosis. Other members of the mammalian LDLR gene family are: LDLR-related protein (LRP), very low density lipoprotein receptor (VLDLR), apolipoprotein E receptor 2 (apoER2), and megalin (6 and Refs therein). Further, cubilin, the intrinsic factor-B 12 receptor, also exerts an extraintestinal function, facilitating endocytosis of HDL (7). Most of these receptors bind and import not only lipoproteins but multiple ligands, such as amyloid precursor protein and various proteases and their inhibitors. Specifically, the extracellular matrix protein *reelin* binds the ectodomain of

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Correspondence and reprint request to Dr George N. Chaldakov, Division of Electron Microscopy, Medical University, B G-9002 Varna, Bulgaria. Tel.: 359 52 454 394, Fax: 359 52 222 584, E-mail: chaldakov@yahoo.com

both VLDLR and apoER2, and thereby is critically involved in the neurotopogenesis in the brain (6,8,9). Furthermore, cubilin, megalin, and p39 receptor-associated protein also play important roles in the biology of neurons. In addition, cholesterol can also affect neuronal development (3,10) and, curiously enough, statins, a group of HMG-CoA inhibitors that are widely used in atherosclerosis therapy, exhibit neuroprotective properties (11).

While numerous studies demonstrated that perivascular sympathetic nerves are associated with spontaneously hyper tensive rats, their role in atherosclerotic lesion formation is largely ignored despite several studies suggest an inverse relation between the density of these nerves and the deve lopment of atherosclerosis (2). Recently, gene knockout and targeted overexpression have been used to generate models of disordered lipoprotein metabolism and atherosclerosis. The most extensively characterized of these models are apoE and LDLR knockout mice. ApoE-deficient mice (12) and cholesterol-fed rabbits/rats (13,14) also develop neuronal abnormalities. Principally, the neuronal abnormalities related to deficiency of lipoprotein receptors, as well as neuropathies related to dys-lipidemia, could also be associated with low levels of neuro-trophic factors, as shown for NGF in diabetic neuropathy (15). Thus, the question remains as to whether lipoproteins and/or their receptors might affect the neuronal development through alterations in the secretion and/or signaling of neurotrophic factors. For example, caveolin, a coating protein of endocytic, plasma membrane cholesterol-dependent, organelle called caveolae, regulates neurotrophin signaling (16), whereas caveolin (17) and LRP (18) expressions are upregulated by NGF. And BDNF regulates *reelin* expression in neuronal deve lopment (19). Nonetheless, genetically-modified models of disordered lipoprotein metabolism could be further examined, in order to see whether nerves, including perivascular sym pathetic nerves, are affected. These considerations taken together suggest that in cardiovascular research, the targets for lipid/glucose metabolism-associated molecules should no longer be considered only vascular wall cells but also peri vascular nerves.

NEUROTROPHIC FACTORS AND LIPID AND GLUCOSE METABOLISM

Recent years witnessed an increased knowledge of the roles played-by neurotrophic factors in the biology of a large number of nonneuronal cells. The potential role of neurotrophic factors in the lipid and glucose metabolism of nonneuronal cells has just recently emerged. For example, NGF, which shares a striking structural homology with proinsulin (20), and LIF exert effects on the lipid metabolism in both adipocytes and hepatocytes (21,22). Similarly, LIF and ciliary neurotrophic factor stimulate hepatic triglyceride secretion (23), and LIF increases LDLR expression in liver cells and decreases serum cholesterol and LDL levels (24), and therby inhibits atherosclerosis development (25). It is also noteworthy that *(i)* BDNF (26) and mast cells (27), known to secrete multiple neurotrophic factors, are implicated in the glucose and lipid metabolism, and (//) pancreatic beta cells secrete and respond to NGF (28). These findings suggest neurotrophin-mediated metabotrophic functions, thus further implicate these molecules in cardiovascular disease and related disorders, such as metabolic syndrome.

As outlined above, there are certain interactions between NGF and caveolin (16,17). An additional comment about caveolin needs a special attention. First, both the structure and the function of caveolae are crucially dependent on plasma membrane cholesterol (4,5). Second, oxidation of cholesterol leads to migration of caveolin, from the plasma membrane to the Golgi complex, and hence inhibition of caveolae-mediated process called potocytosis (4,5). Third, folate is one of the principle molecules that is imported by caveolae (4,5). Fourth, high plasma levels of homocysteine are among the known risk factors for atherosclerosis (29); since homocysteine metabolism is closely linked to that of vitamin B12, one may keep in mind that an important function of cubilin (7) is the import of vitamin B12. All these possibilities could be further explored, using multiple transgenic animal models of neurotrophic factors/ receptors, in order to see whether the lipid, glucose, and homocysteine metabolism are also affected.

„SHALL WE DANCE": A CHALLENGE OF FIELD MIXING

The findings presented here suggest a complex arrangement between cholesterol, lipoproteins/receptors, nerves, and neurotrophic factors and the pathobiolgy of cardiovascular disease. Mixing fields is a challenge that promises high rewards, for both scientists and science alike. Metaphorically, as in the song "Shall we dance", from the American movie "Anna and the King", our hypothesis suggests an invitation for vascular biology and neurobiology to *dance round in a ring* of neurolipidology, in the study of atherosclerosis and related disorders.

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