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Lipids keeps shrinking with aging and neurodegeneration

I remember when my Biology teacher at the secondary school introduced us for the first time to the biochemical components of the living cells. I was immediately fascinated by the elegant code making of the nucleic acids, the intricate design of proteins and the metabolic versatility of carbohydrates. In contrast, lipid functions did not look so fascinating being a fluid structure surrounding all the rest of the molecules. Obviously, I was wrong.

The brain is one of the fattiest organs in the body. Brain lipids develop a plethora of functions, from being structural building blocks and docking sites, mediators in neural communication, synaptic transmission and signal transduction, regulators of neurogenesis and gene expression and preserving membrane functional domains. Lipid structures are dynamic, their relative composition changing in response to several different causes, from diet and mood to neurodegenerative diseases associated with aging.

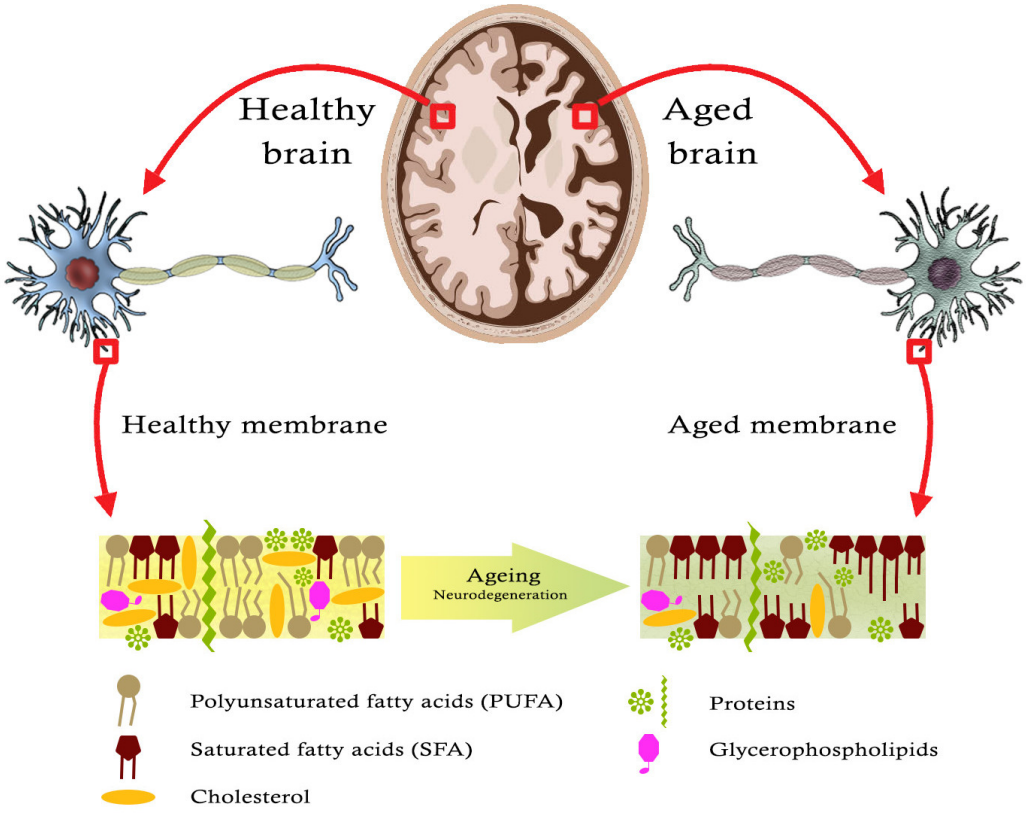

Fig. 1. Brain ageing may generate some subtle changes in the composition of neuronal membranes. In particular, some lipid classes including polyunsaturated fatty acids, saturated fatty acids, cholesterol and glycerophospholipids may alter their composition. Consequently, some proteins integrated into membrane lipid microstructures may modify their activities and functionality. Ultimately, neuronal membrane molecular changes may enhance aging and neurodegenerative diseases.

Lipids comprise over 50% of the nerve cell membranes, sorted out in eight different classes with different biochemical and biophysical properties. Among them, locally sourced and recycled cholesterol is a major component of myelin sheaths, neuronal and astrocyte membranes, and it is a precursor of steroid hormones and neurosteroids. Fatty acids are variably sized structural lipids, with the long-chain polyunsaturated fatty acids or LCPUFAs being also highly abundant in neuronal membranes and myelin, where they participate in some physico-chemical properties such as fluidity and plasticity. Glycerophospholipids are the major phospholipids of the brain, with different polar groups determining five main kinds. Finally, sphingolipids are versatile protein-binding lipids that ensure the stability and functionality of proteins in the membrane, from ion channels to transduction proteins and molecular receptors, and serve as precursors of lipid mediators and regulators of gene expression.

When combined in specific ratios and relative percentages, all these lipids create the cholesterol- and sphingolipid-enriched “lipid rafts”, multimolecular platforms associated to a variety of physiological functions. Within these membrane microdomains, many proteins are anchored through lipid binding that confer stability. Consequently, protein stability in these microstructures is highly dependent on the lipid homeostasis. Indeed, alterations in lipid classes’ balance may compromise lipid rafts’ functionality.

Presently, it has been established that brain lipidomics is exposed to changes throughout lifespan, generally decreasing the lipid content after 50 years old. These modifications are different for distinct lipid species. For instance, cholesterol synthesis rate steadily decreases during adulthood in the whole brain. In parallel, cell membranes become more rigid and increase their viscosity. In this sense, different groups including us have demonstrated that changes in cholesterol levels of lipid rafts may cause aberrant protein-protein interactions and multimolecular rearrangements harmful to the neuronal physiology.

Many other lipid raft components, such as receptors and channels may undergo alterations with aging and, for instance, these molecular changes may exacerbate the progression of age-related neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson disease (PD). Thus, some neuropathological hallmarks of these diseases, such as APP and α-synuclein, interact with lipid rafts, a phenomenon that may contribute to toxic protein aggregation observed in these pathologies.

The brain lipidome is vast and complex. Characterizing the precise nature of lipids and protein species in lipid rafts and other functional microdomains, the dynamic of their interactions and their changes with aging, disease and epigenetic factors may provide essential tools for accurate diagnosis and therapies, ultimately improving our quality of life.

Daniel Pereda, Raquel Marin
Laboratory of Cellular Neurobiology, Department of Basic Medical Sciences, School of Health Sciences, Universidad de La Laguna, La Laguna, Spain

Publication

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Fátima Mesa-Herrera, Lucas Taoro-González, Catalina Valdés-Baizabal, Mario Diaz, Raquel Marín

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