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Review

Membrane raft domains and remodeling in aging brain

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ABSTRACT

Lipids are the fundamental structural components of biological membranes. For a long time considered as simple barriers segregating aqueous compartments, membranes are now viewed as dynamic interfaces providing a molecular environment favorable to the activity of membrane-associated proteins. Interestingly, variations in membrane lipid composition, whether quantitative or qualitative, play a crucial role in regulation of membrane protein functionalities. Indeed, a variety of alterations in brain lipid composition have been associated with the processes of normal and pathological aging. Although not establishing a direct cause-and-effect relationship between these complex modifications in cerebral membranes and the process of cognitive decline, evidence shows that alterations in membrane lipid composition affect important physicochemical properties notably impacting the lateral organization of membranes, and thus microdomains. It has been suggested that preservation of microdomain functionality may represent an effective strategy for preventing or decelerating neuronal dysfunction and cerebral vulnerability, processes that are both aggravated by aging. The working hypothesis developed in this review proposes that preservation of membrane organization, for example, through nutritional supplementation of docosahexaenoic acid, could prevent disturbances in and preserve effective cerebral function.

Contents

Abbreviations: Aβ, amyloid-β peptide; AD, Alzheimer's disease; APP, amyloid precursor protein; CNS, central nervous system; DHA, docosahexaenoic acid; LSR, lipolysis stimulated lipoprotein receptor; PL, phospholipid; PSEN, presenilin; PUFA, polyunsaturated fatty acid; SM, sphingomyelin.

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1. Introduction

The characterization of biological membranes has considerably evolved over the past 20 years. Today, it is widely accepted that the membrane is composed of two co-existing liquid phases: a liquid disordered and a liquid-ordered, the latter constituting the well-known microdomains, or rafts. Although today the microdomain hypothesis is generally accepted, several recent studies question the relevance of the lipid domain hypothesis when applied to the biological context [1,2]. Over the years, studies of model membranes have repeatedly demonstrated that molecular composition of bilayer membranes is central to the generation and properties of microdomains [3–5]. At physiological temperatures, biological membranes are typically in a liquid state, and moreover, certain interactions between specific lipids lead to formation of microdomains that are organized into liquid-ordered domains called lipid rafts [6,7]. Interestingly, lipid-related diseases and/or nutritional imbalance can modulate the lipid composition of cell membranes, and thus the organization of rafts. Research from our laboratory and others indicate that these alterations are partly responsible for neuronal disturbances that can have consequences on cerebral functions.

2. Membrane raft domains

In 1997, Simons and Ikonen were the first to propose a molecular mechanism for lateral heterogeneity of biological membranes. According to these authors, the molecular basis for the raft model lay in the preferential lateral association of long-chain saturated sphingolipids and cholesterol within the exo-leaflet where cholesterol filled the voids between sphingolipid molecules [8].

Since 2006, rafts have been presented as extremely dynamic, small-sized domains (10–200 nm) playing important roles in the compartmentalization of diverse cellular processes. Rafts are not only characterized by their compositional heterogeneity, but are typically enriched in sphingolipids and sterols. Studies have shown that, under specific conditions, small rafts can stabilize and grow into larger platforms. The growth of these platforms is likely due to specific protein-protein and protein-lipid interactions, leading to the lateral segregation of molecular components in the cellular membrane [9]. The presence of raft-specific proteins, such as flotillins or caveolins, are thought to promote the stability of microdomains [10].

3. Roles of rafts in neuronal membranes

Today, rafts are considered as key players in endocytosis and signal transduction, being involved in particular in the endocytosis of the interleukin-2, high-affinity IgE and insulin receptors [11]. The role of rafts in exocytosis has also been extensively reported. For example, the concentration of certain SNARE complex proteins [12], involved in the fusion of synaptic vesicles and release of neurotransmitters such as syntaxins, SNAP-23, SNAP-25 and VAMP-2, is reported to be up to 25 times higher in rafts [10]. Furthermore, rafts are thought to play an important role in synaptic signaling, as demonstrated by the enrichment of synaptic proteins, such as SNAP [13] and PSD in rafts of rat forebrain synaptic membranes and phaeochromocytoma PC12 cells [14]. Cerebral, and in particular neuronal, function can also be affected due to raft-dependent neurotransmitter transporter activity and trafficking, as is the case for choline and serotonin in cells stably expressing the respective transporters [15,16]. Through lateral segregation of membrane-associated proteins, rafts also play a role in the regulation of protein-protein interactions. On the one hand, clustering of proteins within rafts statistically favors their interaction. On the other hand, inclusion of a particular protein within rafts prevents its interaction with proteins located outside of rafts or in distinct sub-populations of rafts. This latter situation results in inhibition of signaling complex assembly and subsequent activation of cascade events [17,18].

Recruitment of receptors into rafts can be necessary for activation of specific signaling pathways, as in the case of the activation of TrkA receptor by nerve growth factor (NGF), or TrkB receptor by brain-derived neurotrophic factor (BDNF), which occurs in rafts [19–21]. Other examples described a ligand-induced relocation of membrane receptors in various cell types. Indeed, the EGF (epidermal growth factor) receptor locates outside of rafts when activated by its ligand, as shown in b82 and NR6 mouse fibroblasts [22], whereas IGF (insulin growth factor) receptor is recruited into rafts upon treatment of human hepatoma HuH7 cells by insulin [23]. Moreover, the NGF (nerve growth factor)-activated (phosphorylated) and palmitoylated TrkA and $p75^{NTR}$ receptors are clustered in the caveolae-like domains of the plasma membrane in mouse 3T3 fibroblasts and in PC12 cells treated with their ligand, but not after caveolae disruption by filipin [24]. Recently, SH-SY5Y cells were used as dopaminergic neurons to demonstrate that the neuroprotective effect of GDNF (*glial cell line-derived neurotrophic factor*) is influenced by the relocation of NCAM-140 into rafts, which can be suppressed by palmitoylation inhibition [25]. In summary, rafts are involved in the regulation of numerous cellular processes, such as the activation of receptors, signal transduction, and signaling pathways. For this reason, rafts are sometimes described as signalosomes, and thus as recruitment, or interaction, platforms for receptors activated by ligand binding [26,27]. Considering the central roles played by rafts in neuronal signaling processes, particularly in synaptic function, modifications in the properties of rafts can thus be expected to adversely affect neuronal function.

4. Impact of aging on neuronal membranes

Cerebral aging is generally acknowledged as a complex process involving multiple factors (for review, [28–30]). We are especially interested in dietary factors, whose impact on the brain function is increasingly recognized. Cholesterol-rich and high fat (saturated)/high sugar diets, such as the Western diet, are indeed regarded as risk factors for metabolic disorders (obesity, type-2 diabetes, hypercholesterolemia and dyslipidemia) correlated to cardiovascular diseases, to brain aging and dementia [31–33], as well as to high incidence of Alzheimer's disease (AD) [34]. The deleterious effects of such diets are widely documented. For instance, cognitive alteration associated with neuroinflammation and oxidative stress were observed in rat hippocampus after short-term (3 weeks) exposure [35]. High saturated fat/high sugar and cholesterol-rich diets were also described to promote β-secretase activity, which increases amyloid-β (Aβ) peptide production and neurotoxicity while accelerating cognitive decline in mice exposed to Aβ, including the Tg2576 mouse used as a model for Alzheimer's disease [30,34,36–38]. In human, diet-induced hypercholesterolemia was associated with higher risk of late dementia [39–41], although confusing data were reported on the potential benefits of statins [42–45]. Altogether, these data demonstrate that dietary factors, lipids in particular, can significantly affect brain functions and exert pro-aging effects on neuronal membranes. Indeed, long-term exposure to nutritional risk factors can cause variations in molecular composition and concentration of cerebral lipid membranes, which in turn lead to neuronal vulnerability and the development of pathological conditions. Based on our previous work and on available literature, we have developed the hypothesis that these alterations affect the organization of the cerebral

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