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ROLE OF CHOLESTEROL IN THE AGING BRAIN

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Abstract: Cholesterol is an essential component of cell membranes and is critical for cell survival and performance.The Central nervous system (CNS) contains nearly 23% of total body cholesterol even though it represents only 2.2 % of total body weight. Cholesterol is required by the brain for active axonal growth, synapse formation and remodelling. Changes in the level of cholesterol are seen to occur in the brain in aging and in neurodegenerative diseases including Alzheimer's disease (AD). In this article, we review the role of cholesterol in normal brain function as well examine the changes associated with hypercholesterolemia and aging. Understanding the causes and consequences of these changes would help to design strategies to delay cognitive decline associated with aging and neurodegenerative diseases.In view of the increased longevity seen, this would go a long way to help reduce the morbidity associated with these conditions in the increasing geriatric population.

Key words: Cholesterol, aging, brain.

Cholesterol is an essential component of cell membranes playing an important role in the maintenance of cellular homeostasis and transmembrane communication within and between cellular compartments (1). Cholesterol synthesis is a multi- step process occurring mainly in the liver and intestine involving the conversion of acetate into cholesterol. The rate limiting reaction in cholesterol biosynthesis is catalysed by 3-hydroxy-3 methylglutaryl CoA reductase (HMGCoA). Since cholesterol is insoluble in water, it is transported in blood complexed with lipoproteins of different size, composition and function (2).

Cholesterol is a key regulator of membrane lipid structure and fluidity and its turnover is strongly correlated with body fat. Cholesterol turnover is higher in obese subjects as compared to lean individuals and the excess body fat correlates significantly with the daily production of cholesterol (3). Cholesterol present in the brain exists in two pools—70% of total brain cholesterol is present in myelin sheaths of white matter and is metabolically stable. The other less abundant pool, comprising about 30% of total brain cholesterol is found in plasma and subcellular membranes of neurons and glial cells within the gray matter. The unesterified cholesterol found here is metabolically active (4).

Even though the CNS represents only 2.2% of body weight, it contains about 23% of total body cholesterol. The cholesterol in the brain is in complete isolation from the cholesterol present in the body due to the presence of the blood-brain barrier(BBB). The half life of brain cholesterol is 6 months to 5 years in contrast to plasma where it is a few hours (5). Cholesterol is required by the brain for active axonal growth, synapse formation and remodelling, and is derived primarily from astrocytes via the synthesis and secretion of apo E associated cholesterol. It has been suggested that neurons during development can synthesize most of the cholesterol they need for growth and synaptogenesis. However, as they mature there is an impairement in this process and are dependent on cholesterol provided by astrocytes (1, 6). Since cholesterol has structural features that make membranes more rigid, maintaining an optimum level of cholesterol is essential for membrane fluidity and neuronal function as it influences the process of neurotransmission. Cholesterol also enhances the efficacy of presynaptic transmitter release, facilitating dendritic differentiation and promoting redistribution of glutamate receptors. It is also crucial for synapse generation since it increases the number of synaptic vesicles containing high levels of cholesterol (7). Cholesterol in addition is considered essential for remodelling neuronal membranes and growing new terminals in response to a neurodegenerative insult. If cholesterol is not supplied to astrocytes, neurotransmission is deleteriously affected. It has been suggested that the absence of cholesterol leads to failure of formation of lipid rafts, which are essential for intracellular signaling as they concentrate the signalling pathways at membranes. Thus absence of cholesterol causes loss in synaptic endings and dendritic spines (8).

The synthesis of cholesterol in the brain occurs mainly

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in the oligodendrocytes and astrocytes. The oligodendrocytes generate cholesterol for the myelination process, which is critical for the insulatory properties of myelin, while the astrocytes produce cholesterol for neuronal cells via the synthesis and secretion of Apo E associated cholesterol. Apo E is one of the major apolipoproteins in plasma and the principal cholesterol carrier protein in brain. While plasma Apo E originates predominantly from the liver and macrophages, brain ApoE is synthesized locally by the astrocytes.The plasma pool of Apo E does not appear to exchange with the brain pool due to the presence of BBB (5). Apo E is known to play a key role in spatial learning and memory process. Studies with transgenic mice lacking Apo E (Apo E -/-) have demonstrated that the loss of Apo E increases behavioural deficiencies, oxidative stress and synaptic dysfunction (9, 10). Infusion of Apo E in such mice reverses the spatial and memory learning impairement caused by the lack of apo E (11).

Aging is a risk factor for the development of neurodegenerative disorders. A decrease in the weight and size of the human brain occurs during aging, due to reduction in neuronal size, synaptic number and both these parameters correlate with cognitive impairement (12). A decrease in the content of cerebral cholesterol is seen throughout life, primarily due to the loss of axons in cerebral cortex (13). Thus cognitive decline observed during aging could be related to the decrease in synaptic transmission and attributable to age related decrease in brain cholesterol.These changes could precede frank dementia by several years.

Hypercholesterolemia, commonly observed during aging can damage the endothelium of the microvasculature, causing a decreased blood flow, thus increasing the possibility of cognitive impairement. Abnormal cholesterol metabolism during aging leads to increased plasma levels of total and LDL- cholesterol, due to increased intestinal absorption coupled with a decreased conversion to bile acids.Though it would appear that circulating cholesterol levels have minimal contribution to brain cholesterol due to the presence of blood brain barrier (BBB), several studies show evidence to the contrary. It has been demonstrated that besides other mechanisms, the BBB is permeable to some hydrophobic molecules such as sterols, hydroxylation of which increases the rate of passive diffusion across the BBB (5). It has been observed that there is a significant net uptake of circulating 27-hydroxy-cholesterol (27-OH cholesterol) by the brain which is in direct proportion to the levels of circulating plasma cholesterol. Correspondingly, this is followed by an efflux of another oxysterol 24S-hydroxycholesterol in the opposite direction. Though there have not been many studies regarding the association of high total cholesterol and dementia, a study conducted by Anstey KJ on 1893 and 4793 participants evaluated for cognitive decline and cognitive impairement respectively who were followed up for 3-29 years, showed an increased risk of dementia with a high mid life total cholesterol. However, there was no evidence supporting an association between high late life cholesterol and dementia (14). Similar findings were observed in a study conducted by Solomon A and co workers on 1449 participants aged 65-79 years over a 21 year follow up. A high midlife total cholesterol represented a risk factor for more severe cognitive impairment later in life (15). A more recently published prospective data by Strand BH et al for the Norwegian County Study (NCS) on 48,793 participants who were followed for 35 years showed a clear cut association of dementia deaths with increased cholesterol levels(>7.80 vs 5.20 mmol/l).The association remained after adjustment for other vascular risk factors and educational level. The authors concluded that people with high cholesterol levels in midlife were at an increased risk of dying from or with dementia later in life (16). Subjects with hypercholesterolemia also have a 20 times increased risk for brain infarction and cerebrovascular diseases as compared to the general population (17).

A positive correlation is observed between plasma cholesterol levels and the incidence of Alzheimer's disease (AD) (18, 19). AD is a neurological disorder characterized by an abnormal accumulation of amyloid β (Aβ) peptide. Puglielli and co workers found that cholesterol ester levels directly correlated with Aβ production both in cell culture and in vivo. They suggested that acyl coenzyme A-cholesterol acyltransferase (ACAT), an enzyme that catalysed the formation of cholesterol esters modulated the generation of Aβ through the tight control of the equilibrium between free cholesterol and cholesterol esters (20). Data strongly suggest that there is a direct relationship between net sterol balance across neurons which seem to dictate the rate of processing of APP (amyloid precursor protein) to Aβ peptide. When the pool of cholesterol in neurons is reduced, the rate of formation of Aβ is decreased (21). Neuropathologic analysis done on animal models have indicated that hypercholesterolemic diet significantly increased Aβ load by increasing both number and size of deposits. Also, the levels of total Aβ strongly correlated with both plasma and CNS total cholesterol (22).

A high fat/high cholesterol diet impairs memory in normal mice and induces neuroinflammation, glial activation, increased expression of cytokines along with markers of oxidative stress (TNF, IL-1β, IL-6, iNOS and COX2). Neuroinflammatory changes in hypercholesterolemic mice are closely correlated with behavioural changes suggesting that cholesterol induced neuroinflammation may play a causal role in memory dysfunction (23). High cholesterol levels in plasma are hypothesized to cause cerebrovascular dysfunction in brain thus triggering the activation of perivascular microglia with scavenger functions (24). The recruitment

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of immune cells to the inflamed brain arterioles may initiate a series of events leading to neurodegeneration, synaptic and cognitive dysfunction, along with increased permeability of BBB.

Several studies have shown that a high fat diet increases the rate of generation of reactive oxygen species(ROS) along with protein oxidation in the brain of rodents (25, 26). ROS interact with proteins, lipids and nucleic acids modifying their structure and function. Hypercholesterolemia increases the generation of ROS, facilitating the development of neurodegenerative diseases through increased oxidant production. This finding has been corroborated by Aytan N, on rabbits who were fed a high cholesterol diet had increased serum levels of protein carbonyl and malondialdehyde accompanied by an increase in protein oxidation parameters in the hippocampus, suggesting that specific neuropathological changes occurred during the feeding of a high cholesterol diet (27).

Clinical and epidemiological data suggest that lowering cholesterol levels with HMG-CoA reductase inhibitors(statins) reduce coronary events.Lowering circulating cholesterol creates a cholesterol gradient across BBB leading to an efflux of 24-S hydroxycholesterol from the brain. Statins also reduce cytokine production by neurons, glia and endothelium (28). Statins reduce the lipoprotein oxidation and ameliorate free radical injury, both of which are seen during reperfusion injury following an ischemic cerebral event. Statins were also associated with a lower risk of dementia in individuals 50 years or older, independent of the presence or absence of untreated hyperlipidemia as reported by Jick and co-workers (29). There have been conflicting reports about the benefits of statin therapy in AD.While Woolozin and colleagues report their findings of a large observational study, demonstrating the association of statin therapy with a 60-73% ($P < .001$) lower prevalence of AD as compared to the total population (30). However, more recently Reitz C in a randomized clinical trial observed no beneficial effect of statin therapy on AD (31). Potential adverse effects of statins appear to be increased risk of intracerebral hemorrhage and cognitive impairement with prolonged use (32).

Cholesterol thus appears to have a clear role in the pathogenesis of age-related dementia and AD. Development of potential newer targeted drug treatments, are an important area for future research which could hold promise in the treatment of neurodegenerative diseases

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