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Review Articles

Review: Brain Lipid Changes in Some Diseases of the Central Nervous System

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In this review, evidence for the alterations in brain lipid composition in some diseases of the central nervous system (CNS) is presented. Various changes are documented in postmortem and in vivo studies in: Alzheimer's disease, cerebral ischemia, Niemann-Pick disease type C, multiple sclerosis, encephalopathy, Fabry disease, Tay-Sachs disease, Sandhoff disease, progressive supranuclear palsy, Huntington's disease, Parkinson's disease. The modifications observed concern the total lipid fraction and the membrane-associated lipids. The alterations vary depending on methods employed for the lipid analysis, selection of the lipids measured and the calculation of data.

Key words: lipid changes, neurological diseases, central nervous system.

Recent studies have suggested that lipids play an essential role in realizing the specific functions of the CNS. Numerous investigations demonstrate changes in brain lipid composition in different functional and pathological states of the CNS. Lipid changes are reported in ageing brains and in brains treated with toxic substances, neurotrophic drugs and under experimental functional conditions-hypokinesia, hyperkinesia and training [4, 23, 29].

The studies of changes in brain lipid composition in some diseases of the CNS are of great interest in order to make clear the role of the lipid changes in the pathogenesis of certain diseases. A great number of investigators have focused on the alterations in brain lipids in Alzheimer's disease, cerebral ischemia, Niemann-Pick disease type C and multiple sclerosis.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized pathologically by cortical atrophy, neuronal loss, excessive formation of neurofibrillary tangles, and deposition of β-amyloid in neuritic plaques.

A number of lipid modifications have been reported in connection with AD [6, 7, 18, 25]. G u a n et al. [6] analyze all phospholipids and their ether subclasses from the frontal cortex, hippocampus and the white matter of AD brain by high performance liquid chromatography and gas chromatography. The total phospholipid content is significantly decreased in both the frontal cortex and hippocampus of AD-affected brains

(20% and 10%, respectively).This change is essentially explained by a selective decrease (20-30%) in phosphatidylethanolamine (PE) and phosphatidylcholine (PC) in frontal cortex. A similar but less pronounced change is observed in the hippocampus. No significant modification in these phospholipids is detected in the white matter. No clear changes are observed in phosphatidylserine (PS), sphingomyelin (SPH), phosphatidylinositol (PI), and cardiolipin (CL) in all three regions when control and AD samples are compared. The authors conclude that the lower content of PE is due to a specific decrease in the plasmalogen subclass. Phosphatidylethanolamine plasmalogen is also the only lipid exhibiting major structural modifications: a significant decrease in polyunsaturated fatty acids and oleic acid as well as a shift of the aldehyde pattern from 18:1 to 18:0.

The findings of Guan et al. are similar to those, obtained in other studies. Pettergrew et al. [18] have demonstrated alterations in brain membrane phospholipid metabolite levels in Alzheimer's disease. The changes in phospholipid metabolite levels correlate with neuropathological hallmarks of the disease and measures of cognitive decline. The nuclear magnetic resonance study of Folch extracts of autopsy material reveals significant reductions in AD brain levels of PE and PI, and elevations in SPH and the plasmalogen derivative of PE. In superior temporal gyrus, there are additional reductions in the levels of diphosphatidylglycerol (DPG) and phosphatidic acid (PA). The authors suggest that the present findings could possibly contribute to an abnormal membrane repair in AD brains which ultimately results in synaptic loss and the aggregation of Aβ peptide.

There are data for changes in the levels of cholesterol in AD. Recent studies have suggested that cholesterol, an important determinant of the physical and the chemical state of biological membranes, plays a significant role in the development of Alzheimer's disease. The relative fluidity of the total brain lipid membranes is influenced by the level of cholesterol and the addition of Aβ results in a decrease in the overall vesicle fluidity [25]. The observations reveal too an inverse correlation between membrane cholesterol level, and Aβ-cell surface binding and subsequent cell death. These results collectively suggest that Aβ-cell surface interactions are mediated by cellular cholesterol levels, the distribution of cholesterol throughout the cell, and membrane fluidity.

There are not enough data for sulfatide changes in AD. Han et al. [7] analyze the sulfatide content of brain tissue extracts by electrospray ionization mass spectrometry from subjects whose cognitive status at time of death varies from no dementia to very severe dementia. All subjects with dementia have AD pathology. The results demonstrate that sulfatides are depleted up to 93% in gray matter and up to 58% in white matter from all examined brain regions from AD subjects with very mild dementia, whereas all other major classes of lipid (except plasmalogen) in these subjects are not altered in comparison to those from age-matched subjects with no dementia.

Several articles present results suggestive of increased peroxidation, but data are contradictory on the areas of the brain affected. Balázs and Leon [3] measure levels of the thiobarbituric acid (TBA)-reactive substances (TBARS) in 12 different brain regions from AD patients and controls and show increased TBARS in frontal lobe. In contrast, Lovell et al. [12] find increased TBARS in the hippocampus, pyriform cortex, and amygdala. Palmer and Burns [17] report increased levels of TBARS in the inferior temporal cortex of AD subjects, but not in the superior temporal gyrus, inferior parietal lobule, superior frontal gyrus, or occipital cortex. Subbarao et al. [20] report that AD is associated with increased basal and iron-induced formation of TBARS in the AD frontal cortex (but not the cerebellum).

Brain lipid changes are engaged in research during cerebral ischemia, too. Ischemia is known to increase the catabolism of membrane phospholipids in brain. There is a

rapid release of fatty acids [8], diglycerides [1], and lysophospholipids [11]. During ischemia, ATP levels decrease to ~5% of control values [15] and after 5 min of reperfusion return to 80% of starting values. K a t s u r a et al. [10] demonstrate the major fatty acid release and collapse in ion gradients occur at ~90 s, when the ATP concentration decrease is maximal. During reperfusion, oxygenated derivatives of arachidonic acid are generated and are thought to contribute to brain edema.

Lipid peroxidation products (LPPs) and phospholipid composition are studied in a model of four-vessel occlusion in rats in homogenates of cortex, striatum and hippocampus after 30 min forebrain ischemia and following 1, 5, 10, 15, 30, and 180 min of recirculation [13]. Major modification of LPPs is found after shorter reperfusion time. Significant decrease is found in the homogenates of cortex. The irreversibility of changes in PS, PE and SPH is noted in the hippocampus after longer reperfusion periods. According to the results, the authors suggest that early reperfusion period seems to be highly critical in the development of ischemia-reperfusion induced neuronal damage.

W e n d e r et al. [24] study the pattern of free sterols in the white matter in an experimental model of global ischemia induced in rats. They show that the percentage of lanosterol happens to decrease sharply following the ischemic state and other sterols, typically occurring in maturating brains and absent in the control brain specimens from adult rats, happen to appear. The appearance of these forms of free sterols in the postischemic brain is interpreted as a biochemical exponent of regeneration processes occurring in the white matter membranes arrest.

Numerous studies demonstrate lipid changes in Niemann-Pick disease. V a n i e r [21] reports that lipids, more particularly glycolipids, are studied in brain tissue from eight cases with proven Niemann-Pick type C (NPC), ranging from 21 fetal weeks to 19 years of age. In gray matter, the concentrations of the total cholesterol, SPH and total gangliosides are within the normal range in all cases. In white matter, a severe loss of galactosylceramide and other myelin lipids is prominent in patients with the neurological severe infantile form or the late infantile form of the disease, but only a slight decrease is observed in patients with a juvenile neurological onset. Analysis of the ganglioside profiles and study of minor neutral glycolipids reveal striking abnormalities, although not present at the fetal stage. In cerebral cortex, gangliosides GM3 and GM2 show a significant increase, 10-15-fold and 3-5-fold the normal level, respectively. A prominent storage of glucosylceramide, lactosylceramide and gangliotriaosylceramide is observed, with 10-50-fold increases from the normal concentration. The fatty acid composition of these glycolipids suggests that they have a neuronal origin. While ganglioside changes are essentially similar in gray and white matter, changes of the neutral glycolipids are only minimal in the latter. Data emphasize that, apart a varying demyelinating process brain lipids abnormalities are essentially located to the gray matter.

Studies of the lipids in multiple sclerosis (MS) demonstrate that the total phospholipid content of MS myelin, determined by phosphorus, is the same as that of normal myelin. F e w s t e r et al. [5] report that there is no difference in the PE content and PE quantity of normal appearing white matter isolated from normal or MS cases. They report on normal values for the plasmalogens and this confirms previous reports. Cerebrospinal fluid concentration of SPH doesn't show significant variations. Most of the authors agree with the thesis that the levels of the total cholesterol remain unaltered in MS myelin. Researches document normal values for cerebrosides and sulfatides in MS myelin, although there are single reports on both decreased and increased sulfatide content. J. Clausen and T. Fog using thin layer chromatography find that the percentage of glycolipids in the liquor (cerebrosides + sulfatides) is highest in MS (three-fold the normal values) and the ratio glycolipids/lecithin is 2.5.

The glycolipid content in MS is studied by other authors too. Zaprianova et al. [28] determine the relative distribution of gangliosides in the serum of patients with MS and healthy subjects. They find that there is a significant increase of GM1 and GD1a, and a decrease of GM3 proportion in the serum of relapsing-remitting MS patients (RRMS) during their first MS attack. The RRMS patients in relapse with a long duration of the disease have a significant decrease of GM1 and an increase of GD1a portion in the serum. An increase of GD1a, one of the major brain neuron ganglioside fraction, suggests the neuron injury in the early and with a long duration RRMS. The finding of an increase of GM1, the main human myelin ganglioside, during the first MS attack in RRMS patients confirms previous evidence for the possible involvement of gangliosides in the early pathological course of demyelination in MS.

Zaprianova et al. [26, 27] report significant changes of the main brain gangliosides (GM1, GD1a, GD1b, GT1b) in brain and in spinal cord in chronic relapsing experimental allergic encephalomyelitis induced in the Lewis rats, that is an experimental model of MS. These results give support to the concept concerning the involvement of gangliosides in autoimmune demyelination in MS.

While brain lipid changes in AD, cerebral ischemia, NPC and MS have received widespread attention in this area of study, relatively few investigators have focused on the brain lipid changes in some rarely spread diseases of the CNS.

Changes of red cell membrane phospholipid composition are studied in children with different neurological disorders – cerebral palsy, organic CNS damages and perinatal encephalopathy [22]. The percentage of PC and, in some cases, of phosphoglycerides increase depending on the diseases type. According to the authors, the above changes are determined by craniocerebral innervation disturbances and concerned mainly the content of PC, PS and PE. The determination analysis establishes that the changes of erythrocytes phospholipid content correlate with clinical state severity and intellectual development of children.

Fabry disease is an X-linked lysosomal disorder characterized by deficient alpha-galactosidase A activity and intracellular accumulation of glycosphingolipids, mainly globotriaosylceramide [9].

Tay-Sachs and Sandhoff diseases are characterized by the absence of β-hexosaminidase activity. GM2 ganglioside fails to be degraded and accumulates within lysosomes in cells of the periphery and the central nervous system [14].

Odetti et al. [16] assess the presence and the amount of lipid oxidation markers by biochemical, immunochemical, and immunocytochemical analysis in mid brain tissue from patients with progressive supranuclear palsy (PSP). They report that the levels of 4-hydroxynonenal (HNE) and TBARS are significantly increased by 1.6-fold and 3.9-fold, respectively, in PSP compared with control tissues.

There are data for putative oxidative damage in the brain of Huntington's disease patients. Alam et al. [2] measure oxidative damage using methods that have already demonstrated the presence of increased oxidative damage in Parkinson's disease, Alzheimer's disease, and senile dementia of the Lewy body type. In contrast to the previous data, no alterations in the levels of lipid peroxidation are found in the caudate nucleus, putamen, or frontal cortex of patients with Huntington's disease compared with normal controls.

There is not enough information on the brain lipid changes in patients with Parkinson's disease. Ross et al. [19] compare levels of the major phospholipid metabolizing enzymes in autopsied substantia nigra with those in non-nigral brain areas of the normal human brain. They report that whereas most enzymes possess a relatively homogeneous distribution, the activity of the major phospholipid catabolizing enzyme phospholipase A2 is low in the substantia nigra. This, coupled with low activity of the

major regulatory enzymes of phospholipid synthesis, in this brain region, suggests that the rate of phospholipid turnover is low in the substantia nigra. Low activity of key phospholipid catabolic and anabolic enzymes in human substantia nigra might result in reduced ability to repair oxidative membrane damage, as may occur in Parkinson's disease.

In conclusion, the present review shows that the brain lipid composition is altered in the above diseases of the CNS. There are two main factors causing the lipid changes. These are the oxidative stress and the genetic defects. Further studies could elucidate the role of brain lipid changes in the pathogenesis of some diseases of the CNS.

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