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Sphingolipids in pathogenesis and treatment of Alzheimer's disease

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It is wellknown that neuronal death is developed according to apoptotic program. Most signaling pathway that trigger apoptosis remain unknown, but the sphingomyelin pathway has been recognized as a ubiquitous signaling system that links specific cell-surface receptors and environmental stresses to the nucleus. This pathway is initiated by the hydrolysis of sphingomyelin via the action of sphingomyelinases to generate ceramide. A number of ceramide species appear to function as second messengers that regulate a large variety of cellular events including differentiation, proliferation, and apoptosis through temporal and spatial coding that can differentially activate signaling cascades.

Taking together the role of free radical reactions in pathogenesis of AD and participation of sphingomyelin pathway in apoptosis of neuronal cells, we have monitored induction of sphingomyelin cycle and activation of lipid peroxidation in rat brain sections after a single intracerebral injection of A-beta(25-35), TNF-alpha and their combination.

We have determined the changes of neutral sphingomyelinase activity (n-SPMase), sphingomyelin (SPM) and ceramide contents and level of lipid peroxide products (conjugated dienes and ketodienes) in the cerebral cortex, hippocampus and cerebellum of rats within 3 hrs and 7 days after A-beta and TNF- alpha intracerebral injection. Maximal changes in SPMase activity, SPM, ceramide contents after single TNF-beta and A-alpha administration were found in the hippocampus, and were less expressed in the cerebral cortex and cerebellum. We found intensification of lipid peroxidation after 3 hrs of peptides injection to the rat brain, but activity of sphingomyelinase was not increased. Remarkable increases in sphingomyelinase activity and content of ceramide were found after 7 days of injection of A-beta(25-35), TNF-alpha.

Increase in the level of peroxide products in hippocampus after 7 days of A-beta and TNF-alpha injection was still remarkable, but combinative injection of TNF and A-beta in the rat brain decreased activity of sphingomyelinase and level of ketodienes to normal level after 7 days . It was proposed that TNF-alpha may protect brain cells from injury induced by A-beta. The role of TNF-alpha in the pathogenesis of Alzheimer disease is unclear, because it has been shown to be involved in both neuroprotection and neurodegeneration depending on doses and age of animals.

It was shown that changes in ratio of SM/ceramide in blood plasma were strongly related to cognitive decline and were the most sensitive predictors of AD progression. (M.M Mielke).

In our experiments with blood plasma lipids samples from patients with AD we investigated influence of drugs with different properties (rivastigmine -inhibitor of cholinesterase and akatinol memantin-inhibitor of NMDA receptors) on changes in ratio of sphingomyelins and ceramides and their molecular spectra. For detection of sphingolipids species we used liquid chromatography/ mass-spectrometry (LC/MS). Sphingolipid levels and spectrum of molecular species of sphingomyelin and ceramide in blood plasma of AD patients, compared to cognitively normal controls, have been found to be altered in the special manner.The most important advantage of LC/MS method is the ability to detect the alteration of each molecular specie of different lipids during medical treatment. It allows to suggest the role of each of these molecules in the evolution and treatment of the disease. It is possible to use the detection of sphingolipids for monitoring of treatment effectivity during Alzheimer's disease with traditional and modern drugs. We suppose also that new drugs, protected brain cells from sphingomyelin digestion could be used for preventing or slowing the onset Alzheimer's disease.

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