REDUCTION OF ETHER-TYPE GLYCEROPHOSPHOLIPIDS, PLASMALOGENS, IN HIPPOCAMPUS IMPAIRS SPATIAL MEMORY IN MICE

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Plasmalogens (Pls) are unique glycerophospholipids with a vinyl-ether bond at *sn*-1 position of the glycerol moiety. It was reported that Alzheimer's disease (AD) patients had reduced Pls levels in the cortex and hippocampus. We previously reported that Pls were anti-inflammatory/ anti-amyloidogenic in lipopolysaccharide (LPS)-induced neuroinflammation and neuroprotective *in vitro*. Furthermore, we show that neuroinflammation reduces Pls in the brain in this congress. In this paper, we confirmed the role of Pls in the hippocampal neurogenesis and memory formation in mice.

Reduction of Pls in mouse hippocampus induced by intrahippocampal injection of lentiviruses encoding sh-RNA against a Pls-synthesizing enzyme, glyceronephosphate O-acyltransferase (GNPAT) gene, impaired spatial memory and decreased expression of brain-derived neurotrophic factor (*BDNF*). Pls-containing diet (0.01%, 0.2-0.25 mg/day) for 6 weeks significantly increased hippocampal Pls and enhanced spatial memory with high expression of phosphorylated (p-) Akt, p-CREB and BDNF, which were blocked by intrahippocampal injection of an Akt inhibitor. The Pls-diet enhanced adult neurogenesis, dendritic spine formation, and hippocampal long-term potentiation. It also increased CREB recruitments onto its putative binding sites of *BDNF* gene. Interestingly Pls-diet induced localization of TrkB in the lipid raft, while it was decreased in *GNPAT* knock-down mice. The involvement of BDNF/TrkB signaling in the Pls-induced enhancement of memory was confirmed by the evidence that intrahippocampal injection of sh-*BDNF*/*TrkB* abolished the effects of Pls-diet. Finally, Pls-drinking (0.025 mg/ml water, 0.15-0.18 mg/day) in triple transgenic Alzheimer's disease model mice for 9 months attenuated accumulation of β-amyloid protein in the hippocampus and improved spatial memory impairment. These findings, taken together, suggest that Pls in hippocampus enhance memory through BDNF-TrkB signaling and reduction of Pls may trigger the memory loss like AD patients.