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学位論文題目	Neuroprotective and cognitive decline-suppression activities of fermented beverage-derived biomaterials（発酵飲料由来機能性素材の神経保護および認知低下抑制作用）
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論　文　内　容　の　要　旨

The potential preventive effects of *Lactobacillus* strains isolated from rice wine lees (sake kasu) and fermented rice bioactive peptide on age-related cognitive decline were investigated in this doctoral dissertation.

Chapter 1 describes the introduction, background literature, and objectives. Aging is a risk for the deterioration of brain function and its main symptom is cognitive deficit. Many factors contribute to the onset of age-related cognitive decline. Oxidative stress is implicated to the pathology of age-related neurodegenerative disease. Aging is associated with the reduction of neurotrophins such as brain-derived neurotrophic factor (BDNF), which regulates not only neuronal development and survival but also long-term potentiation and synaptic plasticity. The dietary intervention has been proposed as an effective therapeutic approach to delay or prevent brain aging and memory impairments. Fermented foods and their by-products may exert potent effects on the brain and cognitive health promotion.

Rice is one of the main cereal crops and staple food for most of the world's population. In some Asian countries, rice is also utilized in the preparation of fermented food products such as Amazake (traditional fermented rice beverage in Japan) and rice wine (sake). In rice wine production, a large amount of residue called rice wine lees containing beneficial microorganisms is generated. However, the potential of rice wine lees as a viable source of probiotics with cognitive-enhancing effects is not yet investigated. The fermentation process allows the production of bioactive peptides from food protein with the aid of microbe's proteases. Several health benefits of Amazake have been reported; however, its neuroprotective effects have not yet been explored.

Chapter 2 deals with the evaluation of preventive effects of long-term dietary supplementation with *Lactobacillus* strains isolated from sake lees on cognitive decline in a mouse model of aging. Fourteen-week-old female senescence-accelerated mouse prone 8 (SAMP8) mice were fed for 43 weeks a standard diet containing 0.1% (w/w) *Lactobacillus casei* subsp. *casei* 327 (L. 327) or *Lactobacillus paracasei* K71 (L. K71). Results showed that age-related memory impairment was reduced in aged SAMP8 mice that were fed an L. K71-supplemented diet. L.K71 group had better cognitive performance compared with the control and L. 327 groups in Barnes maze

and passive avoidance tests. L. K71 long-term administration resulted in increased BDNF protein expression and cAMP response element-binding (CREB) protein phosphorylation in the hippocampus. The levels of serotonin, which stimulates BDNF expression, were also elevated in the serum and brain tissue of L. K71-fed mice.

In Chapter 3, the effects of Amazake fermented rice peptides (FRPs) against scopolamine-induced memory impairment in mice were investigated. Mice were pretreated with FRPs (25 and 100 mg/kg body weight) via intraperitoneal injection for 7 days, followed by intraperitoneal injection of scopolamine. FRP pretreatment improved scopolamine-induced cognitive impairment in passive avoidance test. Compared with controls, the scopolamine-treated mice showed significantly decreased acetylcholine levels and increased acetylcholine-esterase activity in the hippocampus, which was reversed by FRP pretreatment. Scopolamine treatment significantly increased malondialdehyde (MDA) level and decreased superoxide dismutase (SOD) activity but these changes were suppressed by FRP pretreatment. Western blot analysis revealed that FRP treatment significantly attenuated the scopolamine-induced suppression of the protein expressions of BDNF and induced the phosphorylation of CREB protein and extracellular signal-regulated kinase (ERK) in the hippocampus. Among the fractions separated by size-exclusion chromatography, the non-glycosylated peptide fraction of FRP suppressed H_2O_2-induced neuronal damage in SK-N-SH cells by upregulating BDNF expressions. Results indicated that FRP prevented memory impairment and that the underlying mechanism might involve regulation of the cholinergic systems and ERK/CREB/BDNF signaling pathway.

Lastly, Chapter 4 provides a summary and conclusion of the studies. Our findings suggested that long-term administration of a diet supplemented with *Lactobacillus paracasei* K71 isolated from rice wine lees and intraperitoneal administration of Amazake fermented rice peptide could alleviate age-related cognitive decline in mice models of aging by regulating signaling pathways associated to neuroprotection. Taken together, fermented rice beverage-derived biomaterials such as Amazake fermented rice peptides and *Lactobacillus paracasei* K71 isolated from sake lees might have beneficial effects in preventing age-related cognitive dysfunction and dementia among the elderly.