

論文審査の要旨

博士の専攻分野の名称	博 士 (学術)	氏名	JASON DUMAGUING BRAGA												
学位授与の要件	学位規則第4条第①・2項該当														
<p>論 文 題 目</p> <p>Study on novel GABA-increasing dietary factors and their potential role in brain disease prevention</p> <p>(新規 GABA 増加食餌因子と脳疾患予防におけるその潜在的役割に関する研究)</p>															
<p>論文審査担当者</p> <table border="0"> <tr> <td>主 査</td> <td>准教授</td> <td>Thanutchaporn Kumrungsee</td> </tr> <tr> <td>審査委員</td> <td>教 授</td> <td>Noriyuki Yanaka</td> </tr> <tr> <td>審査委員</td> <td>教 授</td> <td>Takuya Suzuki</td> </tr> <tr> <td>審査委員</td> <td>准教授</td> <td>Liao Lawrence Manzano</td> </tr> </table>				主 査	准教授	Thanutchaporn Kumrungsee	審査委員	教 授	Noriyuki Yanaka	審査委員	教 授	Takuya Suzuki	審査委員	准教授	Liao Lawrence Manzano
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<p>〔論文審査の要旨〕</p> <p>Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the brain. Over the past 70 years since GABA was discovered in the mammalian brain, most research has concentrated on its functions within the brain. Due to the blood-brain barrier's impermeability and high peripheral catabolism, roles of circulating or peripheral GABA on the brain has not been widely explored. However, recent research suggests that peripheral GABA is a potent mediator in the gut-brain axis and has the potential to regulate brain functions. This thesis work investigated the potential of dietary factors, specifically prebiotics, to elevate gut and brain GABA levels and their potentials in treating GABA-related brain diseases.</p> <p>In Chapter I, it outlines the critical role of GABA in neurological functions and preventing diseases like epilepsy. The chapter highlights the potential of prebiotics and probiotics to influence brain GABA levels through gut microbiota modulation. Finally, three primary objectives of this thesis work have been addressed, which are to assess if prebiotics can increase peripheral and brain GABA levels, to evaluate synergistic effects of a prebiotic fructooligosaccharides (FOS) and an anti-epileptic drug, vigabatrin, on treating epilepsy in mice, and to explore functions of a brain-specific GABA-containing peptide, homocarnosine.</p> <p>In Chapter II, it demonstrates the impact of dietary prebiotics, i.e., FOS and <i>Aspergillus</i>-derived enzymes (<i>Aspergillus</i>-derived lipase (AL) and protease (AP)), on gut and brain GABA levels in mice. The findings revealed that these prebiotics significantly elevated gut and brain GABA levels, as well as the brain-specific GABA-containing peptide homocarnosine. Specific bacterial genera associated with these changes have been identified. This chapter suggests the potential of prebiotics in treating or preventing GABA-related brain diseases.</p> <p>In Chapter III, the therapeutic potential of the prebiotic FOS in epilepsy treatment has been investigated. Epilepsy is often caused by insufficient GABAergic inhibition or excessive glutamatergic excitation in the brain. Therefore, increasing GABA levels or enhancing GABA-inhibitory signals is a strategy to treat or prevent epilepsy. This study demonstrated that FOS, particularly when combined with the anti-epileptic drug vigabatrin, significantly suppressed epileptic seizures and improved cognitive function in pentylenetetrazol-induced epileptic mice. The</p>															

combination of FOS and vigabatrin led to increased GABA levels in the gut and brain, elevated homocarnosine levels in the brain, and a reduced glutamic acid/GABA ratio. Additionally, the study showed upregulation of antioxidant defense genes (GPX2 and SOD2), downregulation of inflammatory markers (TNF- α and IL-6), and improved tight junction integrity in the brain, suggesting a multi-faceted mechanism by which FOS and vigabatrin ameliorate epilepsy.

In Chapter IV, the study explored the potential roles of endogenous homocarnosine using homocarnosine-deficient mice, specifically carnosine synthase-1 (CARNS1) knockout mice. These homocarnosine-deficient mice exhibited hyperactivity, anxiety, and depression-like behaviors, suggesting a possible role for homocarnosine in mental health and behavior regulation. Despite these behavioral abnormalities, the mice did not show deficits in spontaneous locomotor activity, obsessive-compulsive behavior, olfactory functions, or learning and memory, indicating that homocarnosine may have effects that are specific to mood and behavior.

Chapter V summarizes the key findings of the thesis work. It concludes that prebiotics, such as FOS and *Aspergillus*-derived enzymes, can increase gut GABA and brain GABA/homocarnosine levels, offering potential therapeutic benefits for GABA-related brain disorders like epilepsy. The synergistic effects of combining FOS with vigabatrin in suppressing seizures and improving cognitive function are highlighted. The study suggests that the observed therapeutic effects are due to increased brain GABA and homocarnosine levels, along with enhanced oxidative and anti-inflammatory defenses. Finally, the role of homocarnosine in regulating mood and behavior is demonstrated, pointing to new possibilities for nutritional interventions in managing neurological and behavioral disorders.

Upon thorough review, this thesis has been found to meet the rigorous criteria for evaluation for the degree of Doctor of Philosophy from the Graduate School of Integrated Sciences for Life. Accordingly, the candidate is hereby deemed fully qualified to be awarded the degree of Doctor of Philosophy.