71st ICoMST
GIRONA - CATALONIA - SPAIN
3rd-8th August - 2025

PREVENTIVE EFFECTS OF CHICKEN MARINATED IN SALTED RICE MALT ON DEPRESSION AND INFLAMMATION IN DIABETIC MICE

Haruna Mizutani[1], Kosuke Matsumoto[1], Riko Okada[1], Miyu Matsunaga[1],
Akihiro Kawakita[1], Toshiya Hayashi[1] and Mao Nagasawa[1*]

[1] Faculty of Agriculture, Meijo university, Nagoya, Japan.

*Corresponding author email: mnagasawa@meijo-u.ac.jp

I. INTRODUCTION

Depression is a mental disorder with persistent depressed mood, loss of pleasure and decreased motivation. The recurrence rate with antidepressant treatment remains as high as 60%, making fundamental cure difficult. It is therefore important to establish preventive measures for depression. As depression has various pathogeneses including neurinflammation and impaired neurotransmission, a multidimensional approach is needed to elucidate the underlying mechanisms. Among various factors involved in the pathogenesis of depression, diabetes has been suggested as one potential contributor. Previous studies have reported that approximately 30% of diabetic patients had depressive symptoms [1]. The present study focused on the development of depression induced by diabetes. Understanding the interaction between diabetes and depression could help uncover the biological mechanisms of depression. To achieve this objective, the present study employed a streptozotocin (STZ)-induced diabetic mouse model. STZ, one of the glucose analogues, induces diabetes by selectively destroying pancreatic beta-cells in the islets of Langerhans via glucose transporter (GLUT) 2. Among GLUTs, only GLUT1 is present at the blood-brain barrier and is responsible for glucose transport into the brain [2]. Therefore, STZ does not directly affect the brain. This makes it possible to examine the brain damage caused by systemic changes induced by diabetes.
There is an ongoing debate about the relationship between meat consumption and mental health. However, several studies have reported that eating meat may reduce the risk of depression. Vegetarians and vegans are associated with a higher risk of depression and anxiety compared with meat-eaters [3]. Salted rice malt (Shio koji) is produced by fermenting a mixture of rice inoculated with koji mold, salt, and water. It has strong protease activity, which allows it to break down proteins in the food it is used with. When chicken is marinated with salted rice malt, the proteins are hydrolyzed, potentially producing peptides with new functional properties that may contribute to health benefits. Our previous study revealed that dietary chicken tender marinated in salted rice malt (CRM) solution improved motivational deficits in a neuroinflammation model, suggesting that CRM has anti-inflammatory effects in the brain. In addition, we demonstrated that indomethacin, one of the anti-inflammatory agents, alleviated the depression-like behavior in the STZ model. Based on these findings, CRM may prevent diabetes-induced depression via its anti-inflammatory effects. Therefore, the purpose of the present study was to explore the mechanism by which dietary CRM solution exerts an antidepressant-like effect in an animal model of depression induced by diabetes.

II. MATERIALS AND METHODS

CRM was prepared as follows: chicken tenders, salted rice malt and distilled water (DSW) were mixed in a ratio of 25:5:6 and marinated in a cool and dark place for 3 days. The chicken tenders were washed to remove the salted rice malt, and ground in a mixer together with the same amount of DSW as the chicken tenders. The mixture was heated at a core temperature of 75°C for 1 minute. The collected supernatant after the centrifugation was concentrated and adjusted to the proper concentration.
In the present study, ICR mice (male, 8 weeks old) were divided into three groups (n=10 per group): control (CON) group, STZ group and STZ+CRM group. Mice were intraperitoneally injected of STZ (100 mg/kg) or sodium citrate buffer solution. After an interval of 7 days, daily oral administration of CRM or DSW was initiated on day 8 and continued for 15 days. On day 23, forced swimming test (FST) was conducted to assess depressive-like behaviour 24 hours after the last administration of CRM or DSW. Mice were placed in a cylinder containing 15 cm of water at 25 ± 1°C for 6 minutes. Immobility time was measured during the final 4 minutes, and the total duration was used as an index of depressive-like behaviour. Immobility was defined as a state of keeping their head above water with only small movement in the limbs or head. On day 24, blood and brain samples were collected after 16 hours of fasting. Fasting blood glucose levels were then measured using the collected blood samples. Brain samples were subjected to RNA sequencing (RNA-seq). Total RNA was extracted from the hippocampus using NucleoSpin® RNA (TaKaRa, Japan) according to the manufacturer's instructions. Subsequent RNA-seq library preparation and sequencing were outsourced to Rhelixa (Tokyo, Japan). Immobility time and fasting glusose levels were analyzed by Tukey-Kramer

(p<0.05). Normalization of read counts and detection of DEGs (differentially expressed genes) (FDR < 0.05) were calculated with iDEGES/edgeR-edgeR pipeline using the TCC package [4]. The present study was approved by the Institutional Animal Care and Use Committee of Meijo University (Accession Number: 2024AE5).

III. RESULTS AND DISCUSSION

Fasting blood glucose levels were significantly higher in the STZ group (423.2 ± 63.4 mg/dL) and STZ+CRM group (526.3 ± 65.6 mg/dL) compared with the CON group (127.1 ± 10.1 mg/dL). This result indicates that diabetes was certainly induced by STZ. The results of forced swimming test are shown in Figure 1. Immobility time increased significantly in the STZ group compared to the CON group. Whereas, the STZ+CRM group showed a significant decrease compared to the STZ group and was comparable to the CON group. These results suggest that STZ induced depressive-like symptoms and CRM ameliorated them.

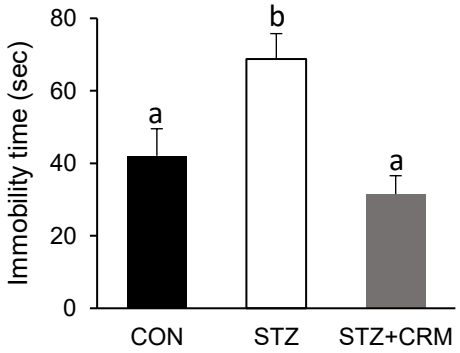


Figure 1. Forced swimming test. Different letters mean significant different at p<0.05 (Tukey-Kramer)

To explore the mechanisms of CRM, RNA-seq was conducted. A total of 26 DEGs were identified: *Etnppl, Pomc, Plin4, Amica1, Mt2, Sult1a1, Rtp1, Pcdhgb8, Arhgef19, 1700015F17Rik, Ctgf, Hif-3a, Ubc, Prss22, Thbs4, C2, Sgk3, Ccr6, Mt1, Btbd17, Gm1821, Tmem181a, Trp53inp1, Hhipl2, Hist1h1c* and *H2-Ea-ps*. Among these, we focused on the inflammation-related genes, *Jaml* and *Hif-3α*. Both *Jaml* and *Hif-3α* were upregulated in the STZ group, but their expression returned to control levels in the STZ+CRM group (Figure 2). *Jaml* is known to regulate T cell activity and promote the production of inflammatory cytokines [5]. *Hif-3α* is upregulated in response to inflammation and has been shown in previous studies to be associated with the NF-κB pathway in the brain [6]. STZ administration may have induced inflammation, while dietary CRM intake may have attenuated this inflammatory response.

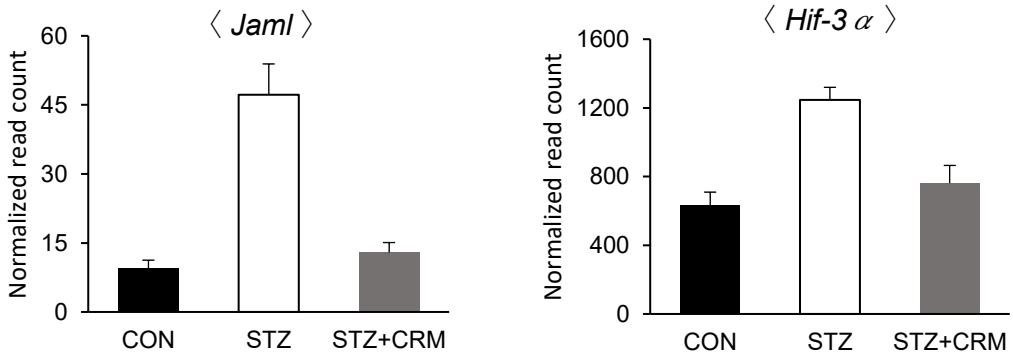


Figure 2 mRNA expression levels of *Jaml* and *Hif-3*

IV. CONCLUSION

The present study showed that dietary CRM intake alleviated diabetes-induced depression-like symptoms in mice. In addition, CRM reduced the mRNA expression levels of inflammation-related genes, suggesting that CRM may exert anti-inflammatory effects. Future studies should investigate whether the DEGs identified in the present study are involved in the pathogenesis of diabetes-induced depression and the antidepressant-like effects of CRM.

REFERENCES

1. Moulton CD, Pickup JC, Ismail K. (2015) The link between depression and diabetes: the search for shared mechanisms. Lancet Diabetes Endocrinol. 3(6):461-471.
2. Koepsell H. (2020) Glucose transporters in brain in health and disease. Pflugers Archiv. 472(9):1299-1343.
3. Dobersek U, Teel K, Altmeyer S, Adkins J, Wy G, Peak J. (2023) Meat and mental health: A meta-analysis of meat consumption, depression, and anxiety. Critical Reviews in Food Science and Nutrition. 63(19):3556-3573.
4. Sun J, Nishiyama T, Shimizu K, Kadota K. (2013) TCC: an R package for comparing tag count data with robust normalization strategies. BMC Bioinformatics. 14:219.
5. Mraz V, Lohmann RKD, Menzel M, Hawkes A, Vaher H, Funch AB, Jee MH, Gadsbøll AØ, Weber JF, Yeung K, Ødum N, Woetmann A, McKay D, Witherden D, Geisler C, Bonefeld CM. (2023) The junctional adhesion molecule-like protein (JAML) is important for the inflammatory response during contact hypersensitivity. Contact Dermatitis. 89(5):323-334.
6. Kumar H, Lim JH, Kim IS, Choi DK. (2015) Differential regulation of HIF-3α in LPS-induced BV-2 microglial cells: Comparison and characterization with HIF-1α. Brain research. 1610:33-41.