Upregulating Effect of Wheat on Brain-Derived Neurotrophic Factor in Human Lung Adenocarcinoma A549 Cells

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Abstract: The neurotrophic hypothesis of depression, that is, a deficiency in hippocampal brain-derived neurotrophic factor (BDNF) leads to depression, has gained widespread acceptance. BDNF is synthesized in various peripheral tissues such as the lung, kidney, liver, heart and testis, besides the brain. Peripheral BDNF can traverse the blood–brain barrier and reach the hippocampus; accordingly, substances that upregulate BDNF production in peripheral tissues may be useful in the treatment of depression. The Mediterranean diet, containing high amounts of whole grains including unrefined wheat, vegetables, fruits, nuts, and olive oil, reportedly reduces the risk of depression. The association between the high consumption of unrefined wheat in the Mediterranean diet and BDNF production in peripheral tissues is unclear. In this study, we investigated the BDNF production capacity of human lung adenocarcinoma cell line A549 and the effect of wheat on BDNF in the cells. Methanol extracts of whole-wheat flour and wheat bran, which are forms of unrefined wheat, increased the BDNF level in the culture medium of A549 cells. However, methanol extract of wheat endosperm had no effect on the BDNF level in these cells. Our findings suggest that wheat bran contains ingredients that upregulate BDNF production in peripheral tissues, and unrefined wheat potentially contributes to the elevation in peripheral BDNF level.

Key words: depression, neurotrophic hypothesis, brain-derived neurotrophic factor, A549 cells, wheat

1 Introduction

Depression has become a prevalent health problem worldwide. The core symptoms of depression include depressive/sad mood, loss of interest in activities, anhedonia, sleep disturbances, lack of energy, melancholy, and suicidal tendencies¹. Clinically, various medications, such as selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors, based on the monoamine hypothesis (i.e., decreased monoamine levels in the brain underlie depression) have been applied to treat depression. However, these drugs are ineffective in approximately 30% of patients with depression² and take several weeks to exert an antidepressant effect³. Therefore, antidepressant agents with a novel mechanism of action are desirable.

In 1997, Duman et al. proposed the neurotrophic hypothesis of depression, that is, a brain-derived neurotrophic factor (BDNF) deficiency in the hippocampus is the underlying cause of depression⁴. BDNF is a member of the nerve growth factor family and plays important roles in neurogenesis, neuroprotection, and synaptic plasticity⁵. BDNF mRNA is translated into a precursor peptide, prepro-BDNF⁶, which is converted into the mature form by several proprotein convertases (PCs), such as furin, PC1, PC5, PC7, and PACE4⁷,⁸.

It has been reported that the administration of BDNF to the hippocampus elicits an antidepressant-like effect in rats⁹. In addition, the mRNA and protein levels of BDNF in the hippocampus are decreased in a rodent model of depression induced by chronic mild stress, restraint stress, corticosterone injection, and olfactory bulbectomy¹⁰–¹³. BDNF is produced in various peripheral tissues such as the lung, kidney, liver, heart and testis, besides the brain¹⁴,¹⁵. BDNF enters the brain from the peripheral tissue via the blood–brain barrier¹⁶,¹⁷. Therefore, substances that upregulate BDNF production in peripheral tissues may elicit therapeutic effects against depression by increasing the

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Accepted March 1, 2021 (received for review November 16, 2020)
The Mediterranean diet, characterized by a high intake of unrefined grains, vegetables, fruits, nuts, seeds, and olive oil, is known to reduce the risk of cardiovascular disease, diabetes mellitus, and cancer. Furthermore, the Mediterranean diet is associated with a reduced risk of depression. Regarding the production of BDNF and consumption of whole grains in the Mediterranean diet, whole grain rye kernel-based bread reportedly increases human plasma BDNF level. Therefore, we speculated that hulls or whole grains other than rye may also upregulate BDNF production. However, to the best of our knowledge, no study has reported that wheat upregulates peripheral BDNF production.

In the present study, we evaluated the effects of methanol extracts of unrefined wheat (whole-wheat flour and wheat bran) and wheat endosperm on BDNF production using human lung adenocarcinoma cell line A549 with BDNF production capacity.

2 Experimental
2.1 Reagents and materials
Dulbecco’s modified Eagle’s medium (DMEM), RNAlater, and TRIzol were obtained from Life Technologies (Carlsbad, CA, USA), and ReverTra Ace was purchased from Toyobo (Osaka, Japan). AmpliTaq Gold 360 Master Mix was obtained from Applied Biosystems (Foster City, CA, USA). The Human Free BDNF ELISA Kit was purchased from R&D Systems (Minneapolis, MN, USA). The primers used in this study (Table 1) were obtained from GeneNet (Fukuoka, Japan) or Greiner Japan (Kanagawa, Japan). Whole-wheat flour and wheat endosperm were purchased from Hara Farm (Kumamoto, Japan), and wheat bran was obtained from YouTech (Hokkaido, Japan). Magnesium chloride hexahydrate, zinc chloride, methanol, 3-(4,5-di-methyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), dimethyl sulfoxide (DMSO), and other reagents were obtained from Wako Pure Chemical Industry (Osaka, Japan).

2.2 Cell culture
A549 cells (JCRB Cell Bank, Osaka, Japan) were cultured in DMEM containing 10% fetal bovine serum at 37°C in a humidified atmosphere with 5% CO₂.

2.3 Reverse transcription-polymerase chain reaction (RT-PCR)
The total RNA was extracted from A549 cells with TRIzol reagent and reverse-transcribed into cDNA using ReverTra Ace. The PCR mixtures containing first-strand cDNA, forward and reverse primers, and AmpliTaq Gold 360 Master Mix were prepared. PCR was performed under the following conditions: an initial denaturation step at 95°C for 10 min, followed by 30 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s, extension at 72°C for 1 min, and a final 7 min extension step at 72°C.

2.4 Measurement of BDNF level in the culture medium of A549 cells
A549 cells were seeded in 96-well plates in DMEM and cultured for 24 h, followed by one wash with phosphate-buffered saline. Fresh DMEM with or without wheat ex-
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tracts or test minerals was added into each well; the cells were cultured for 24 h. Thereafter, the culture medium was collected into a microtube. The level of BDNF in the culture medium was measured using the Human Free BDNF ELISA Kit according to the instruction manual.

2.5 Preparation of wheat methanol extracts

The wheat powder crushed using the Tube Mill 100 control (IKA, Staufen, Germany) was gently agitated in methanol for 12 h at 25 ± 2°C. The supernatant was collected after centrifugation at 15,000 × g for 5 min and dried by spraying nitrogen gas. Each residue was dissolved in DMSO at a final concentration of 40 mg/mL.

2.6 MTT assay

An MTT assay was performed as described in our previous studies.25, 26 Briefly, the cells were seeded in 96-well plates at 1 × 10^4 cells/well and cultured for 24 h. Methanol extracts (0–100 μg/mL) or test minerals (0–100 μM) were added to the culture medium. After 24 h of cultivation, MTT (200 μg/mL) was added to each well, and the cells were cultured for another 4 h. After removing the culture medium, formazan crystals were dissolved in DMSO. The optical density of the samples was measured at 570 nm using a Multiskan FC microplate reader (Thermo Fisher Scientific, Waltham, MA, USA). The values are expressed as the ratio of the optical density of methanol extract-treated cells to that of the control cells.

2.7 Statistical analysis

Values are presented as mean ± standard deviation (SD). Differences between groups were analyzed using the two-sample t-test or one-way analysis of variance, followed by Tukey’s test for multiple comparisons. Differences were considered significant at p < 0.05.

3 Results

3.1 BDNF production capacity of A549 cells

We investigated the mRNA expression of BDNF in A549 cells. BDNF mRNA expression was observed in A549 cells by RT-PCR (Fig. 1A). We then examined whether BDNF secreted from A549 cells could be detected in the culture medium. The level of BDNF in the culture medium of A549 cells seeded at 1 × 10^4, 2 × 10^4, or 4 × 10^4 cells/well density was measured by ELISA. The BDNF level increased in a cell density-dependent manner (Fig. 1B).

Furthermore, we examined the mRNA expression level of enzymes related to the processing of pro-BDNF to BDNF in A549 cells by RT-PCR. A549 cells expressed furin, PC5, PC7, and PACE4 mRNA but not PC1 (Fig. 1C).

3.2 Effects of methanol extracts of wheat on BDNF level in A549 cells

A549 cells seeded at a density of 4 × 10^4 cells/well secreted detectable level of BDNF in the culture medium. Thus, this cell density was selected for subsequent experi-

![Fig. 1](attachment:Fig_1.png)

Fig. 1 BDNF production capacity of A549 cells. (A) mRNA expression of BDNF in A549 cells assessed by RT-PCR. The expected amplified DNA fragment size was 198 base pairs (BDNF). M; DNA marker. (B) BDNF level in the culture medium of A549 cells cultured for 24 h after seeding in 96-well plates at 0, 1, 2, or 4 × 10^4 cells/well. BDNF level was measured using the ELISA. Data are expressed as mean ± SD (n = 6). Two-sample t-test; *p < 0.05. n.d.; not detected (below the detection limit using the ELISA kit used in this study). (C) mRNA expression of furin, PC1, PC5, PC7, and PACE4 in A549 cells examined by RT-PCR. The expected amplified DNA fragment size of furin, PC1, PC5, PC7, and PACE4 was 99, 457, 510, 471, and 456 base pairs, respectively.

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ments to investigate the effect of wheat on BDNF production. To determine the test concentration of wheat methanol extracts, we examined the viability of A549 cells exposed to test wheat extracts at several concentrations (0, 25, 50, and 100 μg/mL) using the MTT assay. Methanol extracts (≤ 50 μg/mL) of whole-wheat flour, wheat bran, and wheat endosperm did not affect the viability of A549 cells (Fig. 2A). However, at 100 μg/mL, whole-wheat flour extract significantly decreased A549 cell viability, whereas those of wheat bran and wheat endosperm did not significantly affect cell viability (data not shown).

Based on the results of the MTT assay, we evaluated the effect of the methanol extracts of wheat at 25 and 50 μg/mL on the BDNF level in A549 cells. The BDNF levels in the culture medium of A549 cells treated with 25 and 50 μg/mL whole-wheat flour or wheat bran were significantly higher than that of the control (Fig. 2B). In contrast, the methanol extracts of wheat endosperm did not affect the BDNF level at any concentration (Fig. 2B).

3.3 Effects of magnesium and zinc on BDNF level in A549 cells

Whole-wheat flour and wheat bran extracts induced the upregulation of BDNF, whereas wheat endosperm ones did not. Importantly, it is known that the content of magnesium and zinc is higher in unrefined wheat than that in wheat endosperm. Therefore, we investigated the effect of magnesium and zinc on BDNF levels in A549 cells. Since magnesium and zinc at 50 and 100 μM did not significantly affect the viability of A549 cells (Fig. 3A), the BDNF levels were measured in the culture medium of A549 cells treated these concentrations. While zinc at 100 μM significantly increased the BDNF level compared with the control, magnesium showed no significant effect (Fig. 3B).

4 Discussion

In this study, we demonstrated that whole-wheat flour and wheat bran upregulated BDNF production in A549 cells. The BDNF level per tissue protein weight was higher in the lung than in the brain. We found that human lung adenocarcinoma cell line A549 expressed BDNF and genes encoding pro-BDNF processing enzymes, such as furin, PC5, PC7, and PACE4 and secreted BDNF into the culture medium. Therefore, we speculated that A549 cells are
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useful for evaluating substances affecting BDNF production. Zhang et al. showed that BDNF was detected in A549 cells by immunoblotting, but not detected in the culture medium by ELISA. In the present study, the BDNF level in the culture medium of A549 cells increased in a cell density-dependent manner and BDNF was undetectable at a cell density of $1 \times 10^4$ cells/well. It is possible that A549 cell density in the study of Zhang et al. was low. Our results suggest that A549 cells may be useful in the identification of peripheral BDNF upregulators. As A549 cells seeded at a cell density of $4 \times 10^4$ cells/well secreted enough BDNF in our study, we decided to screen BDNF upregulators at this seeding density. A549 cells show a high proliferative capacity and can be readily cultured, which are attractive qualities thinking of in vitro systems. However, non-cancer lung cells may also show a high BDNF production capacity because the lung has been reported to produce more BDNF than the brain per gram of tissue. Therefore, in the future, we would like to investigate the usefulness of primary lung cells for the screening of BDNF upregulators. Additionally, we need to compare the usefulness of A549 cells with that of cell line derived from other peripheral

Fig. 3  Effects of magnesium and zinc on BDNF level in A549 cells. (A) Viability of A549 cells treated with magnesium or zinc (0, 50, and 100 μM). Each value represents the viability of treated cells relative to that of the control (0 μM). Data are expressed as mean ± SD (n = 6). (B) Relative BDNF concentration in A549 cells treated with the test minerals. A549 cells were cultured for 24 h in the presence of magnesium or zinc. BDNF level was measured by ELISA. Each value represents BDNF level of treated cells relative to that of the control (0 μM). Data are expressed as mean ± SD (n = 6). Tukey’s test; * p < 0.05.
tissues.

The Mediterranean diet, containing abundant whole grains, vegetables, fruits, nuts, and extra virgin olive oil, has been shown to reduce the risk of depression\textsuperscript{[21-23]}. Among whole grains often consumed in the Mediterranean diet, whole grain rye kernel-based bread has an upregulating effect on human plasma BDNF, but not white wheat flour-based bread\textsuperscript{[24]}. Therefore, we examined the effects of unrefined wheat (whole-wheat flour and wheat bran) and wheat endosperm on BDNF production using A549 cells. The BDNF level was increased by treatment with whole-wheat flour and wheat bran but not wheat endosperm. These results are similar to those of a previous study on whole grain rye kernel and wheat endosperm\textsuperscript{[24]}.

The difference between the effects of unrefined wheat and wheat endosperm could be explained from the perspective of mineral contents. Whole grains include abundant minerals, such as magnesium and zinc\textsuperscript{[27, 28]}; these mineral deficiencies increase the risk of depression\textsuperscript{[30, 31]}. Furthermore, it has been reported that magnesium supplementation is effective in the treatment of depression\textsuperscript{[32, 33]}; moreover, zinc elicited antidepressant-like effects in rodents\textsuperscript{[34, 35]}. The administration of magnesium or zinc upregulates the expression of BDNF in the brain of rodents\textsuperscript{[36-38]}. The magnesium and zinc content in whole-wheat flour is reportedly nearly 6- and 3-fold higher than that in refined wheat, respectively\textsuperscript{[27, 28]}. Furthermore, minerals such as magnesium and zinc were extracted from Telferia occidentalis, a type of evergreen coniferous tree, in methanol\textsuperscript{[29]}. Our results showed that zinc, but not magnesium, increased BDNF levels. Therefore, these results suggest that zinc may contribute to the effect of unrefined wheat extracts on BDNF in A549 cells.

In addition to the mineral content, unrefined wheat contains more phenolic acids (including ferulic acid, p-coumaric acid, sinapic acid, gallic acid, and vanillic acid) than wheat endosperm\textsuperscript{[40, 41]}. These phenolic acids reportedly ameliorated depression-like behavior in previous \textit{in vivo} studies\textsuperscript{[42, 43]}. Furthermore, an ethanol extract of Diptero-carpus alatus (Resin tree) leaf containing these phenolic acids was shown to upregulate \textit{BDNF} mRNA expression in the frontal cortex and hippocampus of stressed mice\textsuperscript{[24]}. Therefore, the phenolic acids contained in whole wheat flour and wheat bran may also be involved in the increase of BDNF levels in A549 cells; this hypothesis, however, must be addressed experimentally in a follow-up study.

The serum BDNF level in patients with depression are reportedly lower than that in healthy subjects, and a lower serum BDNF level is associated with more severe depression symptoms\textsuperscript{[45]}. The serum BDNF level in healthy individuals with stressful occupations is lower than that in individuals who are not regularly exposed to stress\textsuperscript{[46]}. Taken together with our results, whole-wheat flour and wheat bran might have the ability to prevent and treat depression. In the future, it is necessary to examine the effects of these grains on BDNF level \textit{in vivo}.

5 Conclusion

We demonstrated that human lung adenocarcinoma A549 cells expressed \textit{BDNF} mRNA and secreted BDNF; accordingly, this cell line is considered useful in screening upregulators of peripheral BDNF. We revealed that whole-wheat flour and wheat bran extracts increased the BDNF level in the culture medium of A549 cells, and that zinc may be behind this phenotype. Our results suggest that whole-wheat flour and wheat bran have the potential to increase BDNF production and that these grains could be useful food substances to prevent and treat depression.

Acknowledgments

This study was supported by the JSPS KAKENHI (grant number 19K20134) and the Takano Life Science Research Foundation.

Conflict of Interest

The authors declare no conflict of interest.

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