Food-derived antidepressant-like compound ergothioneine promotes neuronal differentiation via activating mTORC1 and neurotrophic factor signaling in neural stem cells.

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Abstract

Clinically used antidepressants have various side effects, and it would be desirable to develop those with minimal side effects. Ergothioneine (ERGO) is a hydrophilic amino acid and abundantly contained in certain foods. Recently, we have reported that ERGO exhibits antidepressant activity after its oral intake and promotes neuronal differentiation in cultured neural stem cells (NSCs) in mice. However, the mechanism underlying the promotion of neuronal differentiation by ERGO has been minimally clarified. The purpose of the present study is to clarify the detailed mechanism to find a novel target for treatment and/or prevention of depression. Especially, we focused on mammalian target of rapamycin complex 1 (mTORC1) signaling known as an amino acids sensor. Exposure of cultured NSCs to ERGO significantly increased phosphorylation of mTOR and p70S6K, which are the downstream positive effectors of the mTORC1 signaling, and decreased that of eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), which is the downstream negative effector of the mTORC1 signaling. On the other hand, the mTORC1 inhibitor rapamycin significantly suppressed the phosphorylation of mTOR and p70S6K by ERGO. Moreover, ERGO significantly increased expression of mRNA and gene product of neurotrophin5 (NT5), and the number of neuronal marker βIII-tubulin positive cells. Furthermore, rapamycin or an inhibitor of tropomyosin receptor kinase B (TrkB), which is a receptor for NT5, significantly suppressed the increase in βIII-tubulin positive cells by ERGO. These results suggest that ERGO may promote neuronal differentiation via activation of mTORC1 and NT5/TrkB signaling in NSCs. ERGO or its derivatives could be a possible candidate for treatment and/or prevention of certain neuropsychiatric diseases including depression because defects in mTORC1 and NT5/TrkB signaling are related with deterioration and/or onset of them.

Persistent glucocorticoid receptor activation reduces M2-like microglia phenotypes without inflammatory signaling.

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Abstract

Objectives: Persistent glucocorticoids (GCs) exposure in chronic stressful stimuli has deleterious effects on the function of neuron and microglia, leading to major depression. In the previous study, we reported that the dysregulation of microglia functional phenotype in chronic stress mice was associated with stress vulnerability and depression relapse. However, the underlying mechanism of glucocorticoid on microglia functional phenotype was not elucidated until now.

Methods: Rat primary microglial cells were enriched in vitro using the shaking method described by Giulian and Baker. After dexamethasone (DEX, glucocorticoid receptor agonist) treatment in primary cultured microglia, the microglia was isolated and qPCR, immunofluorescence study, and western blot were performed to investigate an alteration of microglia functional phenotype. The release factors in microglia were analyzed using ELISA and multiplex assay.

Results: In this study, we found that 72h of DEX treatment reduced fractalkine receptor (CX3CR1) and CD200 receptor (CD200R) in primary cultured microglia while 24h of DEX did not. In addition, the effect was abolished by RU386 (Gc antagonist) co-treatment, suggesting that glucocorticoid receptor (GR) mediates the dexamethasone effect on CX3CR1 reduction in microglia. Interestingly, we found that 72h of DEX treatment decreased both pro-and anti-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-10, TGF-β, IGF-1) expression and secretion in microglia. The NF-kB signaling pathway was not changed by DEX treatment.

Conclusion: Overall, our results suggest that chronic glucocorticoid exposure reduced M2-like phenotype of microglia (CX3CR1 and CD200R) via their specific pathway, which may be involved in stress vulnerability and depression.
Key words: Microglia, Depression, CX3CR1, CD200R, Glucocorticoid

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PS207
Integrated systems analysis of serum proteome profiles of individual drug responses in MDD patients
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Abstract
About 40% of patients treated with antidepressant do not show a response. However, the underlying mechanisms remain unclear and there is no objective test for the prediction of treatment response. The aim of this study was to investigate the proteomic differences between responder and non-responder in patients with major depressive disorder (MDD) who were treated with escitalopram. Fasting blood samples were collected and Clinical Global Impression scale (CGI) was completed at baseline and at day 3, 7, 12, and 42. Five patients who completed the 42days study treatment were included in proteomic analysis. We performed liquid chromatography–mass spectrometry (LC-MS) based proteomics for quantitative profiling of the serum proteomes from seven patients with MDD. Data-independent acquisition (DIA) method was employed for the quantification of each serum proteome. In order to identify proteins that are correlated throughout the antidepressant treatment, the Pearson's correlation coefficients between the protein profiles were calculated and the expression correlation networks (ExprsCorrNetwork) were constructed. The escitalopram network was constructed to identify functional associations between the serum proteins and the drug response. The genes associated with escitalopram were retrieved from PharmGKB database and the 1st interactors of the seed genes were parsed from the protein–protein interaction network of BioGrid. Then, the overlaps between the ExprsCorrNetwork and the escitalopram network were computed. We tested functional associations of ExprsCorrNetwork with the known molecular and physiological evidences of MDD and escitalopram. We retrieved the genes identified in GWAS studies which enrolled patients treated with either citalopram or escitalopram. Between responders and nonresponders, there were differences in protein profile. The profiles of responders were closer at 6 weeks than the profiles of non-responders. R-specific correlations might be related with escitalopram response. Functional associations with MDD and escitalopram should be more investigated.

Keywords: depression, major depressive disorder, escitalopram, response, proteomics

PS208
Preliminary Study on Asymmetry of Theta Quantitative EEG Activity in Patients with Depression and Anxiety Disorders
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Abstract
Depression and anxiety disorders are two of the most common mental illnesses. It is pathognomonic that patients with depressive symptoms show frontal EEG alpha asymmetry while asymmetries related to other EEG wave frequencies have not been consistently reported. The purpose of the study was to examine whether patients who have depression and anxiety disorders together have significant, distinctive characteristics in their EEG activities using qEEG. Twenty-one electrodes of Geodesic 64 channel qEEG device was utilized to measure two groups of participants for five minutes: seven patients with both depression and anxiety disorders (3 males, 4 females, mean age 49.7) in resting state (Eyes closed) and eight normal controls (6 males, 1 female, mean age 24.7). The data were analyzed with NeuroGuide ver. 2.8.5 and were statistically analyzed with the Mann Whitney U-test to compare asymmetries of the two electrodes. The results suggested that theta waves were significantly active at Fp1-Fp2 (p > 0.002), Fp1-C3 (p > 0.001), Fp2-C3 (p > 0.001), Fp2-P3 (p > 0.004), and Fz-C3 (p > 0.002). The preliminary findings demonstrate that frontal and central EEG theta asymmetries may be associated with patient who report both depressive and anxious symptoms. This, in turn, indicates that qEEG can become useful when it is assessed and analyzed objectively and also provide psychiatrists with opportunities to conduct various assessments. The present research will be developed with additional data.

PS209
Changes of cognitive function after escitalopram administration using single word-induced hemoglobin variation as an index
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Abstract
Introduction: Escitalopram is a SSRI, and it can be administered at an effective dose from the first dosing. This drug therapy is effective for rehabilitation in depressive patients. In this study, depressive outpatients attending our hospital performed verbal tasks, and changes of oxy-Hb concentration during the