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PS204

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

Takahiro Ishimoto, Yukio Kato, Yusuke Masuo, Noritaka Nakamichi
Kanazawa University, Japan

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.

PS205

Innate immune molecules activate microglia in mPFC to induce neuronal and emotional changes in mice.

Shiho Kitaoka[1], Tomoyuki Furuyashiki[1], Yuki Imoto[2], Kazuki Nakayama[1], Shuh Narumiya[2], Xiang Nie[1], Atsubumi Ogawa[2], Eri Segi-Nishida[3], Kohei Tanaka[2], Ayaka Tomohiro[1]
[1]Kobe University, Japan, [2]Kyoto University, Japan, [3]Tokyo University of Science, Japan

Abstract

Stress is a risk factor for psychiatric disorders. Repeated stress by social and environmental stimuli alters emotional functions. Although repeated stress activates microglia in various brain regions, it is not known how stress activates microglia and whether activated microglia is involved in behavioral changes induced by repeated stress. Microglia are immune cells and express a variety of pattern recognition receptors including Toll-like receptors (TLRs). Recently, it has been found that cellular stress and tissue damage release endogenous ligands and activate TLRs to induce inflammation. Here, we show that TLR-deficient mice fail to show social avoidance and elevated anxiety induced by repeated social defeat stress. In wild-type mice, single defeat stress increased the number of c-Fos-positive neurons in the mPFC, and this stress response was attenuated with repetition of stress. TLR-deficiency suppressed this attenuation. Repeated stress also shortens the length of dendrites of mPFC pyramidal neurons in a TLR-dependent manner. Immunostaining showed that repeated stress induces microglial activation in wild-type mice, but not in TLR-deficient mice. Furthermore, we recently developed a method to suppress TLR expression in microglia of a specific brain region, and have identified the site of action of TLRs involved in induction of social avoidance by repeated stress. These results suggest that repeated stress activates microglia through TLR, thereby leading to neuronal and emotional changes.

PS206

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

*Min-Jung Park[1)], Hye-Lim Yeo[1)], Min-Jung You[1)], Borah Kim[2)], Min-Soo Kwon[1)] **

[1)] *Department of Pharmacology, School of Medicine, CHA University, CHABIOCOMPLEX, 335 Pangyo, Bundang-gu, Seongnam-si, Gyeonggi-do, 463-400, South Korea.* [2)] *Affiliation: Department of Psychiatry, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea.*

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.