Results: Plasma corticosterone in 3wACTH significantly increased, indicating stress exposure by pharmacological intervention. Three-wACTH showed decrease of time spent in the open arms (elevated plus-maze test), the longer latency to approach a food pellet in the novel environment (novelty-suppressed feeding test) and reduction for sucrose consumption (sucrose preference test). These abnormal behaviors in 3wACTH indicated the anxiety-like and/or depressive-like behaviors, which were observed in 10, but not 6 weeks old. Moreover, adenomegaly observed in 10-week-old 3wACTH compared with control.

Conclusions: These findings suggest that pharmacological stress (namely ACTH administration) during early postnatal period might produce emotional abnormalities such as the anxiety-like and depressive-like behaviors in adulthood but not adolescent, with a critical developmental period.

PS146
Norbin: an emerging player in the pathophysiology and treatment of depression?
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Objective: The neuron specific protein Norbin has recently been implicated in the pathophysiology of depression (Wang et al, 2015). Norbin positively regulates metabotropic glutamate receptor 5 (mGluR5), which is also thought to be involved in depression and has been identified as a novel therapeutic target. The aim of this study was to examine the protein expression of Norbin in a neurodevelopmental rat model of depression, and determine if any alterations in Norbin were associated with mGluR5.

Methods: Brains were extracted from Sprague-Dawley (SD; healthy model) and Wistar–Kyoto (WKY; depression model) rats at postnatal days (PN) 14, 35, and 98 corresponding to juvenile, adolescent and adult time-points. Immunoblots were performed on prefrontal cortex (PFC) and hippocampal tissue to measure Norbin and mGluR5 protein levels.

Results: Norbin was expressed in both the hippocampus and PFC at all three developmental stages in both rat strains. In the hippocampus, there was a reduction in Norbin protein levels in WKY compared to SD rats, specifically at the adolescent time point (-38%). This was associated with a change in mGluR5 expression at this time point; we observed a reduction in mGluR5 dimer levels (-57%) and an increase in mGluR5 monomer expression, which remained in the adult brain (>100%). In the PFC, Norbin was dramatically increased at adolescence and adulthood in WKY rats compared to SD rats (>100%). While mGluR5 monomer levels were increased at adulthood in the PFC, no significant changes in dimeric expression were observed at any time point examined.

Conclusion: These findings provide support for an involvement of Norbin in the pathophysiology of depression. While further studies are required to determine the implications of these differences in Norbin and mGluR5 in WKY rats, targeting mGluR5 or Norbin at adolescence may represent an alternative therapeutic approach for the treatment of depression.

PS147
Gunn rats show depression-like behavior and microglial activation in the hippocampus
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Abstract
Recent studies imply that glial activation play a role in the pathogenesis of psychiatric disorders, such as schizophrenia and affective disorder. Although a number of animal studies have attempted to establish appropriate animal models for these psychiatric diseases, the numbers of established models, which show signs or symptoms relevant to the diseases, are limited. We have previously demonstrated that Gunn rats with hyperbilirubinemia show congenital gliosis and schizophrenia-like behavior. Since it is suggested that major depression involves glial activation, we examined whether Gunn rats show depression-like behavior using the forced swimming test (FST) and the tail suspension test (TST). In addition, we quantitatively evaluated microgliosis in the hippocampus of Gunn rats using immunohistochemistry analysis with the microglial marker ionized calcium binding adaptor molecule (IBA)-1.

We employed male homozygous (j/j) Gunn rats and male Wistar rats as normal control individuals. They were all 7 weeks old. In the FST, rats were placed into the water (25 ± 1 °C) for 15 min. After 24 hours from the habituation, rats were put into the water for 6 min. In the TST, rats were suspended from the tail for 5 min. All the session were recorded by a video camera. The duration of immobility was measured based on the recorded movie.

Both the FST and TST showed that immobility time of Gunn rats was significantly longer than that of Wistar rats, indicating that Gunn rats have depression-like behavior. The quantitative immunohistochemistry analysis using Image J revealed that hippocampal immunoreactivity for IBA-1 was significantly increased in Gunn rats compared to Wistar rats. These results suggest that Gunn rat could be an animal model of depressive symptoms and activated microglia.

PS148
Repeated restraint stress induces alteration in maturation makers of dentate gyrus neurons in BALB/c mice
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Abstract
Stress is widely accepted as a predisposing environmental factor in psychiatric disorders, including depression and schizophrenia. We previously found “immature dentate gyrus (iDG)”, in which almost all the granule cells in the hippocampal dentate
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PS149
Interleukin-18-deficient mice develop dysfunction of hippocampus resulting in depression-like behavior

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Abstract

Objectives: Major depressive disorder (MDD) is a common disorder that has been implicated in marked disabilities in global functioning, anorexia, and severe medical comorbidity, and also known as being closely related to inflammation. We found that interleukin-18-deficient (Il18−/−) mice exhibit dysfunction of the hippocampus resulting in depression-like behavior. To verify the mechanism of MDD, the relation between interleukin-18 (IL-18), which is one of the inflammatory cytokines, and the hippocampus were examined in this study.

Methods: Il18−/− male mice were generated on the C57Bl/6 mice background as previously described (Takeda K, et al. Immunity, 1998). Littermate C57Bl/6 Il18+/+ male mice were used as controls. For behavioral analysis of depression and hippocampal functions, we used -open space swimming test, tail suspension test, and water maze learning were performed. In addition, immuno-staining and electron-microscope were performed for histopathological analyses.

Results: Our behavioral analysis indicated that Il18−/− mice might show the disability of learning and memory comparing to Il18+/+ mice. Moreover, in the hippocampus of Il18−/− mice, the marker of neurogenesis in immunostaining and morphological changes could be observed in the dentate gyrus of the hippocampus.

Conclusions: These findings suggested that deficiency of IL-18 can lead to dysfunction of the hippocampus resulting in behavioral changes, such as those associated with MDD.

PS150
Comparative efficacy of various augmentation strategies for treatment-resistant depression: a meta-analysis of randomized controlled trials

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Abstract

Objectives: Since the introduction of newer antidepressants, there have been great advances in treatments for major depression. However, many patients with major depression have inadequate responses to standard therapy. To date, many studies that investigated the efficacy of various treatment strategies for treatment resistant depression have been conducted. We investigate whether there are differences in the effect size of various augmentation strategies according to the degree of treatment resistance.

Methods: A comprehensive literature search was performed using multiple databases. We performed this meta-analysis using Cochrane review methods. The primary outcome variable of this meta-analysis was response rate in patients with treatment resistant depression who were treated with alternative augmentation strategies in addition to standard antidepressant therapy.

Results: A comprehensive literature search identified 20 randomized controlled trials. The nineteen studies, which included 638 participants, were pooled using a random-effects model to compare the effect sizes among various treatment strategies. We conducted subgroup analyses according to the degree of treatment resistance defined as the number of failed trials during current index episode (TRD 1 and TRD 2 or higher). The seven studies, which included 638 participants, were pooled to compare the effect sizes among various strategies in the TRD 1 trials. Various augmentation strategies for treatment resistant depression included lithium augmentation, antidepressant combination, augmentation with thyroid hormone, pindolol augmentation, augmentation with atypical antipsychotics, augmentation with stimulants. The 8 studies, which included 96 participants, were pooled to compare the effect sizes in the TRD 2 or higher trials. Overall, there was no significant difference in the effect sizes among various strategies in treatment resistant depression in terms of response rates (Response, risk ratio (RR)= 1.45 (95% confidence interval (CI) 1.25 to 1.67); Test for subgroup differences, Chi2=2.57, df=5, P=0.67, I2=0%). For TRD 1 trials, there was no significant difference in the effect sizes among various strategies in treatment resistant depression in terms of response rates (Response, risk ratio (RR)= 1.43 (95% confidence interval (CI) 1.10 to 1.85); Test for subgroup differences, Chi2=3.69, df=3, P=0.30, I2=18.7%). For TRD 2 or higher trials, there seemed to be a significant difference in the effect sizes among strategies. The efficacy for atypical antipsychotics has well-founded evidence (RR=1.52 (95% CI= 1.33 to 1.74),