

Symposium | Schizophrenia : [Symposium 75] Current Topic of Biological Psychiatry: Synapse, Glia and Inflammation

📅 Sat. Sep 27, 2025 3:50 PM - 5:20 PM JST | Sat. Sep 27, 2025 6:50 AM - 8:20 AM UTC 🏛️ Session Room 4 (Large Hall B)

[Symposium 75] Current Topic of Biological Psychiatry: Synapse, Glia and Inflammation

Moderator: Takahiro A. Kato (Department of Psychiatry, Hokkaido University Graduate School of Medicine), Shigenobu Kanba (Kyushu University)

[SY-75]

Current Topic of Biological Psychiatry: Synapse, Glia and Inflammation

Takahiro A. Kato¹, Shigenobu Kanba², Sota Kyuragi², Si Tianmei³, Masaaki Iwata⁴ (1. Hokkaido University (Japan), 2. Kyushu University (Japan), 3. Peking University (China), 4. Tottori University (Japan))

[SY-75-01]

Reverse translational research using human blood induced microglia-like (iMG) cells: Are microglia causing fires in the brain?

*Takahiro A. Kato¹ (1. Department of Psychiatry, Hokkaido University Graduate School of Medicine (Japan))

[SY-75-02]

Development of biomarkers of hikikomori focusing on inflammation and microglia

*Sota Kyuragi¹, Takahiro A Kato² (1. Kyushu University (Japan), 2. Hokkaido University (Japan))

[SY-75-03]

Study the Immunoinflammatory mechanisms of Depression: The role of protein tyrosine phosphatase receptor type Z1 and astrocyte-microglia interactions

*Tian-Mei Si^{1,2} (1. National Clinical Research Center for Mental Disorders(Peking University Sixth Hospital/Institute of Mental Health) (China), 2. The Key Laboratory of Mental Health, Ministry of Health (Peking University) (China))

[SY-75-04]

Antidepressant Effects of β -Hydroxybutyrate Based on the Neuroinflammation Hypothesis of Depression and Its Potential for Clinical Application

*Masaaki Iwata¹ (1. Tottori University (Japan))

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Keywords : inflammation、microglia、NMDA

In this symposium, we will discuss the current topic of biological psychiatry especially focusing on neuro-glia interactions and brain inflammation.

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[SY-75-01] Reverse translational research using human blood induced microglia-like (iMG) cells: Are microglia causing fires in the brain?

*Takahiro A. Kato¹ (1. Department of Psychiatry, Hokkaido University Graduate School of Medicine (Japan))

Keywords : microglia、inflammation、reverse-translational research

Microglia play crucial roles of inflammation in the brain. Postmortem brain analysis and PET imaging analysis are two major methods to assess microglial activation in human, and these studies have suggested activation of human microglia in the brain of patients with various neurological and psychiatric disorders. However, by using the above methods, only limited aspects of microglial activation can be measured. We have originally developed a technique to create directly induced microglia-like (iMG) cells from fresh human peripheral blood monocytes adding GM-CSF and IL-34 for 2 weeks, instead of brain biopsy and iPS technique (Ohgidani, Kato et al. Sci Rep 2014). Using the iMG cells, dynamic morphological and molecular-level analyses such as phagocytosis and cytokine releases after cellular-level stress exposures are applicable. Recently, we have confirmed the similarity between human iMG cells and brain primary microglia by RNAseq (Tanaka, et al. Front Immunology 2021). We believe that patients-derived iMG cells will take a role as one of the important surrogate markers to predict microglial activation in patients with various neurological and psychiatric disorders. In this symposium, we will introduce our latest findings using iMG cells with such patients. We have already revealed previously-unknown dynamic pathophysiology of microglia in patients with Nasu-Hakola disease (Sci Rep 2014), fibromyalgia (Sci Rep 2017), rapid-cycling bipolar disorder (Front Immunology 2017) and Moyamoya Disease (Sci Rep 2023). The iMG cells can analyze both state- and trait- related microglial characteristics of human subjects by repeated blood collection, which is especially valuable because majority of psychiatric disorders express situation- and time- oriented symptoms. We believe that the iMG techniques shed new light on clarifying dynamic molecular pathologies of microglia in a variety of neuropsychiatric and other brain disorders.

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[SY-75-02] Development of biomarkers of hikikomori focusing on inflammation and microglia

*Sota Kyuragi¹, Takahiro A Kato² (1. Kyushu University (Japan), 2. Hokkaido University (Japan))

Keywords : hikikomori、inflammation、iMG cells、hsCRP、bilirubin

Objective: Hikikomori, a severe form of social withdrawal now listed in the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-5-TR), is a recognized global issue that frequently co-occurs with various psychiatric disorders. Our previous studies have identified key psychological traits, such as high suicidal ideation and diminished social connection. Despite these insights, the biological basis of hikikomori remains largely unclear, and biomarker studies are limited. This study aims to identify the biological characteristics of hikikomori by investigating biomarkers using both plasma analysis and a blood-derived cellular model. **Methods:** Participants were recruited from the Mood Disorder/Hikikomori Clinic at Kyushu University Hospital and were diagnosed with hikikomori if they met the criterion of spending almost all their time at home for more than six months. Following informed consent, we collected peripheral blood samples and detailed clinical data. These samples were utilized for acquiring biochemical data and obtaining peripheral blood mononuclear cells. These cells were subsequently differentiated into induced microglia-like (iMG) cells, a patient-derived cellular model used to analyze microglial function.

Results: Our analyses revealed a distinct psychobiological profile for patients with hikikomori. Psychologically, they exhibited not only high suicidal ideation but also pronounced loneliness, anhedonia, and psychomotor retardation. Biochemically, patients had significantly higher levels of high-sensitivity C-reactive protein (hsCRP) and significantly lower levels of total bilirubin. Furthermore, the analysis of iMG cells revealed different gene expression phenotypes in hikikomori patients. **Discussion:** Our findings suggest that hikikomori has a distinct pathophysiological background involving inflammation and increased susceptibility to oxidative stress as indicated by elevated hsCRP levels, reduced bilirubin levels, and iMG gene phenotypes. In psychiatric practice, where objective data is scarce, this combined methodology offers a powerful strategy for developing objective biomarkers and identifying novel therapeutic targets for this complex condition.

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[SY-75-03] Study the Immunoinflammatory mechanisms of Depression: The role of protein tyrosine phosphatase receptor type Z1 and astrocyte-microglia interactions

*Tian-Mei Si^{1,2} (1. National Clinical Research Center for Mental Disorders(Peking University Sixth Hospital/Institute of Mental Health) (China), 2. The Key Laboratory of Mental Health, Ministry of Health (Peking University) (China))

Keywords : Neuroinflammation、Chronic stress、Cytokines、Astroglia-microglia interaction

Major depressive disorder (MDD) is a highly disabling mental disorder characterized by persistent low mood, anhedonia, and cognitive impairment. Its etiology is complex, and the neuroinflammatory responses are considered a critical pathogenic mechanism of MDD, with the homeostatic balance of inflammatory cytokines and the immunoregulatory functions of glial cells being essential for maintaining normal neuroimmune function. Protein tyrosine phosphatase receptor type Z1 (PTPRZ1) has recently been identified as a key molecule involved in the regulation of neuroinflammation, and its genetic variations have been associated with the pathogenesis of MDD. We used the post-witness social defeat stress model, which has been validated for studying the immune mechanisms of MDD. We found the notably increased the expression of PTPRZ1 protein, the significant enhancement of PTPRZ1 phosphatase activity in the hypothalamus and the higher levels of proinflammatory cytokines in stressed mice. The behaviors and immune response could be reversed by both the typical antidepressants (fluoxetine) treatment and administration of the PTPRZ1 phosphatase inhibitor MY10. And additionally, MY10 treatment significantly inhibited the overactivation of microglia in the hypothalamus of stressed mice, reduced the number of M1 pro-inflammatory microglia, and increased the number of M2 anti-inflammatory microglia. This study first unveiled the critical role of PTPRZ1 in the neuroimmune regulation of the hypothalamus in chronically stressed mice. The Immune-inflammatory and astrocyte-microglia interactions play the important role in the pathology of MDD. this immune response. Additionally, this study found that the PTPRZ1 phosphatase inhibitor MY10 modulates microglial polarization and effectively alleviates depressive-like behaviors in stressed mice. These findings provide new theoretical insights into the pathogenesis of MDD and offer potential therapeutic targets for developing novel PTPRZ1-based treatment strategies.

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[SY-75-04] Antidepressant Effects of β -Hydroxybutyrate Based on the Neuroinflammation Hypothesis of Depression and Its Potential for Clinical Application

*Masaaki Iwata¹ (1. Tottori University (Japan))

Keywords : Depression、Inflammation、beta hydroxybutyrate

The monoamine hypothesis, which attributes depression to reduced function of neurotransmitters such as serotonin and norepinephrine, has long dominated the understanding of depression's pathophysiology. However, many patients show limited response to monoaminergic treatments, highlighting the need for alternative models. Recently, the neuroinflammation hypothesis has emerged, suggesting that chronic stress and environmental factors activate microglia in the central nervous system, triggering the release of pro-inflammatory cytokines like IL-1 β and TNF- α . These disrupt neuroplasticity and may underlie depressive symptoms. We focused on β -hydroxybutyrate (BHB), an endogenous ketone body with anti-inflammatory properties, as a novel therapeutic approach. BHB is produced in the liver during fasting, exercise, or ketogenic diets and crosses the blood-brain barrier to act within the central nervous system. In animal models of stress-induced depression, BHB administration significantly improved depression-like behaviors. Mechanistically, BHB suppressed activation of the NLRP3 inflammasome and reduced brain IL-1 β expression. It may also enhance BDNF expression via HDAC inhibition, contributing to both anti-inflammatory and neuroplasticity-promoting effects. Based on these findings, we are currently conducting a specified clinical trial in patients with depression to evaluate BHB's therapeutic potential. As BHB is already used as a dietary supplement and demonstrates high safety and oral bioavailability, it is a promising candidate for clinical application. This research supports a shift from the monoamine-based model to a molecularly informed neuroinflammatory paradigm of depression, offering a foundation for novel, mechanism-based interventions. Further multi-institutional collaboration is ongoing to clarify BHB's efficacy and mechanisms, aiming toward its integration into personalized psychiatric care.