Psychosis symptoms following aberrant immunity in the brain

Akitoshi Ozaki¹, Yuki Yamawaki¹, Gen Ohtsuki¹

Neuroinflammation in the brain is thought related to the emergence of various psychoses, although the identifying neural significance, the involvement of immune-cells and lymphocytic activity, and ways for the therapeutic recovery are under the effort of researchers. We recently revealed that the cerebellar anterior lobes showed depression-like modulations: animals with inflammation in the right hemisphere, while inflammation in the left hemisphere induced various forms of neurophysiological modulation of cerebellar Purkinje cells (Yamamoto et al., 2020). The animals with high TNF-α expression level in macrophages is high in the blood samples. The efferent connections from the cerebellum to the thalamic nuclei, red nuclei, and ventral tegmental area were observed in the cerebellar anterior lobes. These behavioral correlations in recent studies of rodent models (Ohtsuki et al., 2020; Figure 1). Notably, the frontoparietal cortex is organized by four regions: fastigial, interpositus, dentate, and vestibular nuclei, which have distinct projections and modulate behavior in different ways. The difference in the behavioral phenotype (i.e., depressive- or autistic-like) may come from the inflamed region in the cerebellum. This gives us a lesson: the psychiatric effects of brain inflammation are not uniform across the brain because of the distinct circuitry, even in the cerebellum. Cerebellar inflammation may also alter dendritic integration of electrical current (i.e., electrophysiology) of Purkinje-cells, via the downregulation of Ca²⁺-activated K⁺-channels (SK2 channels) (Ohtsuki, 2020). Therefore, aberrant inflammation in the cerebellum and resultant neurophysiological modulation cause disruption of distinct regions of the brain via connections.

Psychosis symptoms following aberrant immunity: How does the aberrant immunity occur in the brain? And, what is the chronic effect? Brains in neonatal and developing stages are very vulnerable. It would be true that the phenotype is dependent on the genome-environment interplay. A review study by Brown et al. (2010) had emphasized the role of the prenatal and early-life infection with influenza virus, herpes simplex virus type 2 (HSV2), and Toxoplasma gondii (a parasitic protozoan) is a risk factor for the SCZ among offspring and those affected, as referred in many epidemiologic and translational studies. Infectious RNA viruses; influenza virus, measles virus, Japanese encephalitis virus, human immunodeficiency virus, Rotavirus, West Nile virus, and SARS-Coronavirus-2, and DNA viruses; cytomegalovirus (herpesvirus), and Adenovirus, are known to cause the encephalitis. Microbial and viral infections and resultant encephalitis can cause high cytokine conditions in the brain and in the uterus, and serious inflammation symptoms associated with cognitive dysfunctions. However, the mechanism of these after-effects were not well understood.

Viral infection during pregnancy increases the risk of psychosis to the offspring, such as SCZ, ASD, bipolar disorders, and developmental disorders. In the mouse model, it is known that neonatal infection with influenza virus, herpes, CMV, and early-life infection with influenza virus, herpes, CMV, and early-life infection with influenza virus, CMV, and EHV-1, which results in autism-like behaviors. Therefore, the pathophysiologic effects of brain immune cells, it is problematic if we suppose that the function of immune cells is homogeneous. Rather, microglia and astrocytes have the heterogeneity across brain regions, between the inflamed cerebellum and prefrontal neocortical regions. This study suggested that aberrant immune activity in the cerebellum induces neuronal hyperexcitability of the prefrontal cortex, via cerebello-frontal connectivity (Yamamoto et al., 2019; Ohtsuki et al., 2020; Figure 1). Of note, in the diagnosis of schizophrenia, TNF-α expression level in macrophages is high in the blood samples. The efferent connections from the cerebellum to the thalamic nuclei, red nuclei, and ventral tegmental area were observed in the cerebellar anterior lobes. These behavioral correlations in recent studies of rodent models (Ohtsuki et al., 2020; Figure 1). Notably, the frontoparietal cortex is organized by four regions: fastigial, interpositus, dentate, and vestibular nuclei, which have distinct projections and modulate behavior in different ways. The difference in the behavioral phenotype (i.e., depressive- or autistic-like) may come from the inflamed region in the cerebellum. This gives us a lesson: the psychiatric effects of brain inflammation are not uniform across the brain because of the distinct circuitry, even in the cerebellum. Cerebellar inflammation may also alter dendritic integration of electrical current (i.e., electrophysiology) of Purkinje-cells, via the downregulation of Ca²⁺-activated K⁺-channels (SK2 channels) (Ohtsuki, 2020). Therefore, aberrant inflammation in the cerebellum and resultant neurophysiological modulation cause disruption of distinct regions of the brain via connections.

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developmental timing, and cytokine milieu in rodents and humans. In any case, such psychosocial-like symptoms of rodents, effectors are considered interleukins and interferons from helper T cells and microglia. Regulatory T cells would also contribute. And, those effects are probably without the brain region-dependency but are depending on the immune cells’ localization.

Vascular system and potential therapeutic ways through the metabolism: Although many mental illnesses are certainly thought to be potentially due to a genetic factor, immune and metabolic abnormalities may be phenotypically the cause of many symptoms. Therefore, it might be possible to seek therapeutic targets out of those processes. Present optical microscopy has been remarkably advanced for deep tissue imaging. For example, multiphoton imaging can visualize the capillary blood flow which delivers molecules or reagents into the central nervous system. By expressing fluorescent molecules in endothelial cells of the neurovascular unit in vivo, it would be possible to see relationships between the vascular activity and psychological phenotypes. In the brain, physiologically active eicosanoids, prostaglandins, are involved in functional hyperemia, vasodilation, stress responses, and fever (Furuyashiki et al., 2018). In the cerebellum, cerebellar dysfunction and psychosis, which underlie the cerebello-frontal pathways (Figure 1); so that, if the mechanisms including immunity and metabolism are revealed thoroughly, a therapeutic way could be lit up.

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