学位論文内容の要旨
Abstract of the dissertation

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Studies on behavioral abnormalities and proinflammatory cytokine upregulation under neuroinflammation: Focus on glial cells

(神経炎症下における行動異常と炎症性サイトカイン発現亢進に関する研究―グリア細胞に焦点を当てて)

The monoamine hypothesis has been considered to be an underlying mechanism of mental disorders for more than half a century. Antidepressants and antipsychotics have been developed based on this hypothesis, but many patients are refractory to treatments targeting this regulatory mechanism, supporting the likelihood of other regulatory mechanisms such as the neuroinflammation, neuroplasticity, and neurogenesis hypotheses. In recent years, it has been suggested that neuroinflammation and monoamine are related to each other in terms of the etiology of mental disorders. In the present study, I focus on proinflammatory cytokine production and cell morphology in glial cells as elements linking the monoamine and neuroinflammation hypotheses in terms of the pathogenesis of mental disorders.

Proinflammatory cytokines released by glial cells act not only as immune factors, but also can directly regulate neuronal firing, like neurotransmitters and gliotransmitters. Glial cell processes regulate the levels of releasing factors in the extracellular space including neurotransmitters and cytokines in a spatiotemporal manner via rapid elongation and retraction of their processes in response to stimuli. Furthermore, the enhanced cytokine production and changes in the process morphology of glial cells are characteristic features of neuroinflammation, and are dependent on the degree and progression of inflammation. Thus, proinflammatory cytokines and process morphology of glial cells may regulate the neurotransmission. However, it remains unclear how the pathological characteristics of glial cells in neuroinflammation, especially cytokine production and morphology, progress over time and how they are associated with behavioral abnormalities. Furthermore, many studies have not considered the possibility that changes in monoamine levels may affect neuroinflammation, and the mechanisms by which cytokine production and their morphology are regulated, particularly the involvement of monoamines, is also unclear.

In Chapter I, I aimed to elucidate behavioral abnormalities and the pathophysiology of neuroinflammation using the lipopolysaccharide (LPS)-injected mouse model, which is often used as a model for the neuroinflammation hypothesis. LPS-injected mice after recovery from systemic symptoms exhibited short-term memory impairment in behavioral tests 7 days after injection. Suppression of hippocampal CA1 neuronal activity, increased proportion of immature spines, and transient glial cell activation were observed. Decreased spine density due to enhanced phagocytosis of activated microglia could be responsible for increased immature spines. In Chapter II, the primary cultured astrocytes were used to elucidate the mechanisms by which monoamines regulate proinflammatory cytokine interleukin-6 (IL-6) expression and process formation. It has been found that D1- and D2-like receptors and α_1-AR, in addition to ß-ARs, regulate IL-6 expression, which involves CREB and ERK phosphorylation, in cultured astrocytes. D1- and D2-like receptors and α_2-AR, in addition to ß-ARs, regulate astrocytic morphology. Especially, the high concentrations of dopamine regulate these effects via α- and ß-ARs in addition to dopamine receptors. Furthermore, bidirectional regulation was observed, i.e., the effects of D1-like receptors and ß-ARs were negatively regulated by D2-like receptors and α_2-ARs. These findings can lead to novel understandings of the pathophysiology of mental disorders which demonstrates the relationship between the monoamine hypothesis and the neuroinflammation hypothesis. The findings may provide a basis for the development of new therapies.