学 位 論 文 の 要 旨

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学 位 論 文 名　HYPERBILIRUBINEMIA-RELATED BEHAVIORAL AND NEUROPATHOLOGICAL CHANGES IN RATS: A POSSIBLE SCHIZOPHRENIA ANIMAL MODEL

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論 文 内 容 の 要 旨

Introduction

Idiopathic unconjugated hyperbilirubinemia (Girbert's syndrome,GS) is a relatively common congenital hyperbilirubinemia occurring in 3-7% of the world's population. It was reported that unconjugated bilirubin might be associated relatively with neurotoxicity in the developing nervous system. Patients with schizophrenia show a significantly higher frequency of hyperbilirubinemia than patients suffering from other psychiatric disorders and the general healthy population. We have also observed that patients with schizophrenia frequently have an elevated bilirubin plasma concentration on admission to the hospital. Based on these facts, hyperbilirubinemia may have potentially influential effects on schizophrenia.

The Gunn rat, a mutant of the Wistar strain has been used in several previous studies as an animal model of bilirubin encephalopathy. The Gunn rat has a genetic deficiency in glucronyltransferase. The heterozygous (+/j) rat has approximately 50% enzyme activity,

the homozygous (j/j) rat completely lacks the enzyme. Some Gunn j/j rats have many of the same neurological symptoms and histological lesions that are exhibited by hyperbilirubinemic human newborns. To assess the effects of hyperbilirubinemia on the behaviors, programmed cell death, neuronal protein synthesis activity, and neurogenesis, which are observed in several currently available schizophrenia rodent models, we compared behavioral and neuropathological characteristics of Gunn and Wistar rats.

Materials And Methods

The animals were male severely hyperbilirubinemic j/j, and non-jaundiced +/j male Gunn rats and Wistar rats that were 7 weeks old at the time of experiments.

The behavioral studies were open-field, social interaction and prepulse inhibition (PPI).

The histological studies were terminal transferase-mediated dUTP-biotin nick-end labeling (TUNEL), silver nucleolar organizer region (AgNOR) and Ki-67 staining.

Analysis of variance (ANOVA) with post-hoc Bonferroni's PLSD was used to test for differences in the data of these groups.

Results and Discussion

Compared to Wistar rats, both Gunn j/j and +/j rats showed hyperlocomotion, high sniffing scores. These stereotyped behaviors are supposed to be positive symptoms of schizophrenia. In the social interaction tests, they showed significantly more aggressive behaviors (gnawing, clinching, mounting, and pursuing) and inappropriate social interaction (decreased sniffing and following). And they exhibited impaired PPI. PPI deficits have been proposed as an animal model of the sensorimotor gating impairment characteristic of schizophrenia. It has been reported rats selectively bred for deficient PPI perform poorly in behavioral paradigms used to model negative symptoms of

schizophrenia. Thus, PPI deficits have some relationship to negative symptoms of schizophrenia. The behavioral abnormalities of Gunn rats are similar to those observed in several currently available schizophrenia rodent models.

It has been suggested that the nucleolar AgNOR is directrly proportional to neuronal activity, Ki-67 immunoreactivity is a measure of adult neurogenesis occurring in the subgranular zone (SGZ) of the hippocampus, and TUNEL-labeled cells exhibit the parameter of apoptosis. The numbers of AgNOR and Ki-67-labeled cells were lower and the numbers of TUNEL-positive cells were higher in Gunn j/j and +/j rats than in Wistar rats. Based on the decrease of AgNOR in Gunn +/j and j/j rats in this study, we assume that neuronal cell activities of Gunn rats are significantly impaired than that of Wistar rats. In a human postmortem brain study, the ratio of the apoptotic protein Bax/Bcl-2 was significant higher, and adult neurogenesis was shown to be decreased by using Ki-67 staining in patients with schizophrenia.

The results might indicate that, compared with Wistar rats, not only Gunn j/j but also +/j rats are vulnerable to the effects of many things, such as oxidation, drugs, and the environment, a condition that is similar to schizophrenia.

Conclusion

Even though Gunn +/j rats have not received the same experimental attention as j/j rats due to their lower levels of hyperbilirubinemia, both Gunn j/j and +/j rats exhibited neurological problems that may make them useful as a rodent model of schizophrenia.