Pediatric RESEARCH

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BASIC SCIENCE ARTICLE

Normalizing hyperactivity of the Gunn rat with bilirubin-induced neurological disorders via ketanserin

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BACKGROUND: Severe neonatal hyperbilirubinemia has been known to cause the clinical syndrome of kernicterus and a milder one the syndrome of bilirubin-induced neurologic dysfunction (BIND). BIND clinically manifests itself after the neonatal period as developmental delay, cognitive impairment, and related behavioral and psychiatric disorders. The complete picture of BIND is not clear.

METHODS: The Gunn rat is a mutant strain of the Wistar rat with the BIND phenotype, and it demonstrates abnormal behavior. We investigated serotonergic dysfunction in Gunn rats by pharmacological analyses and ex vivo neurochemical analyses.

RESULTS: Ketanserin, the 5-HT2AR antagonist, normalizes hyperlocomotion of Gunn rats. Both serotonin and its metabolites in the frontal cortex of Gunn rats were higher in concentrations than in control Wistar rats. The 5-HT2AR mRNA expression was downregulated without alteration of the protein abundance in the Gunn rat frontal cortex. The TPH2 protein level in the Gunn rat raphe region was significantly higher than that in the Wistar rat.

CONCLUSIONS: It would be of value to be able to postulate that a therapeutic strategy for BIND disorders would be the restoration of brain regions affected by the serotonergic dysfunction to normal operation to prevent before or to normalize after onset of BIND manifestations.

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IMPACT:

- We demonstrated serotonergic dysregulation underlying hyperlocomotion in Gunn rats. This finding suggests that a therapeutic strategy for bilirubin-induced neurologic dysfunction (BIND) would be the restoration of brain regions affected by the serotonergic dysfunction to normal operation to prevent before or to normalize after the onset of the BIND manifestations.
- Ketanserin normalizes hyperlocomotion of Gunn rats.
- To our knowledge, this is the first study to demonstrate a hyperlocomotion link to serotonergic dysregulation in Gunn rats.

INTRODUCTION

Delivery from in utero low-oxic condition into the oxygen-rich atmosphere lets newborn infants switch their oxygen carrying hemoglobin (Hb) from fetal-type HbF to adult-type HbA, where HbF and HbA are, respectively, hetero-tetramers $\alpha_2\gamma_2$ and $\alpha_2\beta_2$ of α-, β-, and γ-globin-chain subunits.[1,2] While the switching is completed about 1 year after birth, relatively immature livers in infants have to dispose of the neurotoxic bilirubin, a degradation product of hemoglobin, using UDP-glucuronosyltransferase (UGT1A1), a liver enzyme essential for the disposal of bilirubin. Newborn infants having defective UGT1A1 genes are therefore more predisposed to hyperbilirubinemia,[2–5] which is not rare in Asian races.[3,5]

Severe neonatal hyperbilirubinemia has been known to cause the clinical syndrome of kernicterus, as well as the milder syndrome of bilirubin-induced neurologic dysfunction (BIND). BIND clinically manifests itself after the neonatal period in the form of developmental delay, cognitive impairment, disordered executive function, and such behavioral and psychiatric disorders as attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and autism spectrum disorder (ASD).[6–10] In neonatal hyperbilirubinemia, neurotoxic bilirubin in the peripheral blood crosses the blood–brain barrier and binds to such brain regions as the brain stem, basal ganglia, hippocampus, and cerebellum to adversely affect neuro-developmental processes including neurogenesis, myelination, and synaptogenesis during the early developmental stage.[11] Mechanism-based elucidation, however, of the linkage from hyperbilirubinemia in peripheral blood to those disturbances in brain function has still to be carried out.

The Gunn rat is a mutant strain of the Wistar rat but lacking UGT1A1 activity caused by the homozygous defective UGT1A1 gene,[12,13] and hyperbilirubinemia of the rat begins soon after birth and persists for life.[14] The neurological abnormalities and the histopathology of the rat are similar to those of human nuclear jaundice,[15] and the severe clinical symptoms of the rat are extrapyramidal disorders, such as dystonia, seizures, and death.[15]

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