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Presentation Abstract

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Presentation Title: Sp4 hypomorphic mice, a hypoglutamatergic genetic model for schizophrenia

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Abstract:

- Sp4 gene encodes a neuron-specific transcription factor that binds GC-rich DNA in the promoter of most genes. Its expression begins from E9.5 during mouse embryogenesis and persists throughout the adulthood. Sp4 knockout mice display reduced hippocampal size, subtle hippocampal vacuolization, as well as impaired postnatal development of hippocampal dentate gyrus.
- Sp4 hypomorphic mice, expressing 2 to 5% of the level of Sp4 mRNA in wildtype mice, were generated through knocking-in. The mutant mice displayed several intermediate phenotypes relevant to schizophrenia and other psychiatric disorders: deficient sensorimotor gating (prepulse inhibition); impaired memory (fear conditioning, passive avoidance, Barnes maze); increased sensitivity and prolonged responses to ketamine in both locomotion and prepulse inhibition tests.
- Electrophysiological studies found that Sp4 hypomorphic mice displayed reduced LTP in the hippocampal CA1 of brain slice. Awake EEG recording revealed an induction of high frequency gamma oscillation only in the mutant mice injected with ketamine, an indication of increased sensitivity to the NMDAR antagonist.
- Molecular studies demonstrated a reduction of NMDAR1 in the mutant mice, consistent with the behavioral and electrophysiological findings. Impaired NMDAR signaling was also supported by reduced expression of pCREB in Sp4 hypomorphic mice. Decreased expression of GAD67 was also observed.
- Human SP4 gene was deleted in some patients with schizophrenia, supporting the construct validity of Sp4 hypomorphic mice as a hypoglutamatergic model. Moreover, reduced expression of SP4 proteins was reported in the postmortem brains of patients with bipolar disorder. Genetic association studies suggested that human SP4 SNPs associate with schizophrenia, bipolar disorder, and major

depression.

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