The Ottawa Hospital | L'Hôpital d'Ottawa

Research project summary

Mechanisms underlying schizophrenia

- Principal Investigator: Hsiao-Huei Chen
- Awarded $646,425 from the Canadian Institutes of Health Research (CIHR) in May 2017
- Summary reproduced from the CIHR website in the language provided

Clinical Issue: Schizophrenia (SZ) is a debilitating mental disorder affecting young adults. SZ symptoms include early social isolation, cognitive decline prior to episodes of auditory hallucinations, false beliefs and associated anxiety and depression. Current treatments targeting the dopaminergic system remedy psychosis but not other schizophrenia symptoms. The goal is to identify therapeutic targets dysregulated early in the disease process to provide better outcomes for SZ. We have recently discovered a new mouse model of SZ in which the phosphatase enzyme PTP1B is hyperactive in the brain. We also found that in two other commonly used experimentally induced mouse models of SZ this enzyme activity is increased in the affected brain regions. Our previous work showed that hyperactivity of this enzyme disrupts the function of important glutamate receptors on neurons. This can lead to malfunction of dopaminergic circuitry and cause psychosis in humans. Moreover, we reported that hyperactivity of this enzyme also impairs the production of one of the body's own cannabis-like substances (endogenous cannabinoid). Since cannabinoids control how much neurotransmitters are released from neurons, this would further lead to aberrant neuronal activity. Dysregulated levels of cannabinoids in the serum and the cerebrospinal fluid are observed in SZ patients. Our hypothesis is that elevated PTP1B activity is the central mechanism that accounts for functional deficits in the SZ brain. We will test whether targeting this enzyme with a selective inhibitor called Trodusquemine will ameliorate SZ symptoms in two preclinical mouse models. Significance: In Canada, about 1% of the population (~350,000) has SZ. Successful validation of targeting PTP1B to improve SZ in preclinical mouse models can rapidly move to clinical trials since Trodusquemine has already undergone phase 1 clinical trials to treat obesity.

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