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Grant Title: Potential impact of perineuronal net on the pathogenesis of Schizophrenia

Abstract

Aim: Perineuronal nets (PNNs) are highly organized components of the extracellular matrix that surround a subset of mature neurons in the central nervous system. These structures play a crucial role in regulating neural plasticity during development around a time so called critical period. Recent work has revealed the importance of PNNs in protective effects in animal models of neurodegenerative disease and neurotoxicity. PNNs have further been implicated in a number of psychiatric disorders. The etiology of schizophrenia (SZ) is thought to require an interaction between genetic susceptibility and environmental risk factors. A loss of PNNs in the prefrontal cortex has been suggested to contribute to cognitive impairment from postmortem human brain studies of SZ. Furthermore, alternations in parvalbumin expressing interneurons are highly replicated findings in those patients. PNNs are comprised of hyaluronan, chondroitin sulfate proteoglycans (CSPGs) of lectican family, tenascin and link proteins as a core extracellular matrix (ECM). Aggrecan is a major constituent of PNNs.

The aim of this study is to explore the potential impact of perineuronal net on the pathogenesis of Schizophrenia using conditional CNS-knockout (KO) of *Acan* (*Acan* CNS-cKO).

Methods: A genetic model of conditional CNS-specific *Acan* KO was generated by crossing *Acan* floxed mice (*Acan* $^{flox/flox}$) and Nestin (*Nes*)-Cre mice. Measurement of prepulse inhibition (PPI) were performed using 12- to 20- weeks-old male *Acan* $^{flox/flox}$; *Nes*-Cre and control mice. The animal experiment protocols used in this study (OKU-2019384) were approved by Okayama University Animal Research Committee.

Results: 1) In *Acan* CNS-cKO, complete loss of WFA (a Pan-PNN marker) was observed in the cortex of brain. In these animals, immunostaining of other PNN constituents such as brevican, neurocan, Hapln1, and Hapln4 were absent. While mRNA expression of those genes was not affected in KO. These results suggest degradation of core proteoglycans are induced in KO. 2) PPI of startle reflex is a measure of sensorimotor synchoronization. A deficit of PPI has been observed in schizophrenia patients and animals as an endophenotype. PPI test did not show any statistical differences between control and *Acan* CNS-cKO mice. 3) A slight decrease of GAD67 immunolabeling was observed in the prefrontal cortex of KO compared with control. However, more intense studies including other part of cortical regions are required to conclude results. Our study on the role of PNN may provide insights into understanding the etiology of psychiatric disorders.