Neuropsychopharmacology www.nature.com/npp

CORRESPONDENCE

Matrix metalloproteinase 9 levels and parvalbumin positive interneuron dysfunction

Neuropsychopharmacology (2022) 47:429; https://doi.org/10.1038/s41386-021-01048-9

I read with great interest the recent publication by Seitz-Holland et al. [1] in which they report an association of increased serum levels of matrix metalloproteinase 9 (MMP9) and hippocampal volume reduction and negative symptoms in schizophrenia. The authors discuss the role of MMP9 as an essential regulator of neuroplasticity and of the extracellular environment of the postsynaptic part of excitatory synapses and its control of hippocampal and dendritic development. Hence, to the extent that peripheral MMP9 levels reflect central concentrations, their finding points to abnormal increases of MMP9 as a potential factor driving hippocampal pathology in patients with schizophrenia.

However, the authors do not elaborate on another important aspect which may link MMP9 abnormalities to hippocampal and other cortical pathology in patients with schizophrenia. MMP9 is essential for the regulation and organization of perineuronal nets (PPN)—an extracellular matrix (ECM) component - by cleaving and degrading ECM components. PPNs play a critical role in maintaining cell integrity and functioning. They are particularly important for the functioning of parvalbumin-positive interneurons (PVIN) [2]. PNNs regulate survival and excitability of PVINs interneurons and protect PVINs against oxidative stress. Similarly, it has been shown that PNNs regulate the activity of PVINs and gamma EEG activity in the prefrontal cortex [2]. Loss of PNNs around PV cells is associated reduced excitability of PV cells. PNN disruption has been shown to increase membrane capacitance and thus reduce the ability of PV interneurons to fire [3]. Consequently, increased levels of MMP9 have been associated with reductions of PNNs and consequently deficient PVIN functioning [2]. Indeed, genetic reduction of increased MMP9 levels leads to a normalization of PNNs and of abnormal PVIN functioning in a mouse model of Fragile X syndrome [4].

There is a large literature implicating dysfunction of PVINs in schizophrenia and other neuropsychiatric disorders [5]. Second, elegant preclinical studies convincingly demonstrate a key role of PVINs in the generation of gamma oscillation, critical for information processing and cognitive operations [6]. Thus, in schizophrenia and other neuropsychiatric disorders abnormal gamma oscillations point to specific deficits in PVIN functioning. Given the role of MMP9 in the integrity of PNN and PVIN functioning [2], it is tempting to speculate that increased levels of MMP9 should be particularly associated with PVIN dysfunction manifested in abnormalities in gamma oscillations (particularly increased gamma power in resting state EEG together with a decreased phase synchrony). The hypothesis that increased MMP9 levels should be associated with such distinct abnormalities in gamma oscillation and potentially other measures of cortical disinhibition can be easily tested in clinical studies. If proven correct, then MMP9 levels could be regarded as a proxy for PVIN pathologyy in schizophrenia, but also other neurodevelopmental disorders like autism spectrum disorder where PVIN abnormalities have also been implicated. It is also plausible to assume that differences in PVIN pathology may affect the response to specific pharmacological intervention. MMP9 levels could thus prove useful for stratification in clinical pharmacological trials.

FUNDING AND DISCLOSURE

No funding was received for this work. The author declares no competing interests.

ADDITIONAL INFORMATION

Daniel Umbricht[1]
[1]*Xperimed LLC, Klybeckstrasse 130, Basel, Switzerland*
Correspondence: Daniel Umbricht (Daniel.umbricht@xperimed.com)

REFERENCES

1. Seitz-Holland J, Seethaler M, Makris N, Rushmore J, Cho K-IK, Rizzoni E, et al. The association of matrix metalloproteinase 9 (MMP9) with hippocampal volume in schizophrenia: a preliminary MRI study. Neuropsychopharmacology. 2021. https://doi.org/10.1038/s41386-021-00997-5.
2. Carceller H, Guirado R, Ripolles-Campos E, Teruel-Marti V, Nacher J. Perineuronal nets regulate the inhibitory perisomatic input onto parvalbumin interneurons and c activity in the prefrontal cortex. J Neurosci. 2020;40:5008–18.
3. Bosiacki M, Gąssowska-Dobrowolska M, Kojder K, Fabiańska M, Jeżewski D, Gutowska I, et al. Perineuronal nets and their role in synaptic homeostasis. Int J Mol Sci. 2019;20:4108. https://doi.org/10.3390/ijms20174108.
4. Wen TH, Afroz S, Reinhard SM, Palacios AR, Tapia K, Binder DK, et al. Genetic reduction of matrix metalloproteinase-9 promotes formation of perineuronal nets around parvalbumin-expressing interneurons and normalizes auditory cortex responses in developing Fmr1 knock-out mice. Cereb Cortex. 2018;28:3951–64.
5. Ruden JB, Dugan LL, Konradi C. Parvalbumin interneuron vulnerability and brain disorders. Neuropsychopharmacology. 2021;46:279–87.
6. Cho KKA, Hoch R, Lee AT, Patel T, Rubenstein JLR, Sohal VS. Gamma rhythms link prefrontal interneuron dysfunction with cognitive inflexibility in dlx5/6+/- mice. Neuron. 2015;85:1332–43.

Received: 27 April 2021 Accepted: 25 May 2021
Published online: 7 June 2021