Early-life changes in prefrontal cortical function in the MAM model of schizophrenia

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ABSTRACT

Schizophrenia is a common, severe and multifactorial neuropsychiatric disorder, for which current medication mainly focuses on treating the positive symptoms of the disease.

Aim: In our study we aim to identify early-life neurophysiological changes in the methylazoxymethanol acetate (MAM) mouse model of schizophrenia compared to control mice (saline-treated) [1].

Methods: Our experiments include neonatal (P8-P11), juvenile (P15-P21) and adolescent (P40-P45), female and male C57BL/6J mice. MAM or control mice of all groups were decapitated and prefrontal cortical (PFC) brain slices were acquired for extracellular local field recordings, followed by analysis for neuronal oscillations and up state generation present in the recordings. Adolescent MAM and control mice performed the temporal object recognition (TOR) task, and were additionally investigated for $GABA_A$ receptor ($GABA_AR$) reversal potential in PFC through patch-clamp recordings.

Results: We observe a significant reduction regarding the baseline neuronal oscillations of delta, theta, alpha and beta rhythms in neonatal MAM mice, but not in juvenile or adolescent MAM mice, while juvenile MAM mice have increased frequency of up states, compared to controls. In control adolescent mice, ketamine application in PFC brain slices increased the beta and gamma frequencies; however, in MAM adolescent mice ketamine reduced the contribution of these frequencies. Finally, adolescent MAM mice exhibit a significantly reduced discrimination index compared to control mice in TOR task, and a more positive $GABA_AR$ reversal potential.

Conclusion: Early-life alterations of neuronal oscillations and up states generation could affect prefrontal cortical development and lead to cognitive deficits (TOR deficits) observed in adolescent MAM mice.

REFERENCES

[1] Chalkiadaki, K. et al. (2019) 'Development of the MAM model of schizophrenia in mice: Sex similarities and differences of hippocampal and prefrontal cortical function', Neuropharmacology, 144, pp. 193–207.