Regulatory role of hippocampal miR-328 on a mouse model of psychosis combing methamphetamine with electroconvulsive shock

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Background
Methamphetamine (MAP) is a psychotomimetic drug, which can induce abnormal behaviors in mice. On the other hand, to treat major psychoses, electroconvulsive therapy (ECT) has been proved to be a highly effective and safe treatment option. However, the underlying mechanism of ECT remains largely unknown, and there is no research directly addressing the combined molecular mechanisms of miRNAs with the adverse behavioral effects causing by MAP and the therapeutic effects of ECT.

Aims & Objectives
We hypothesize that there are specific miRNAs in brain mediating the changes of behaviors and brain functions after chronic MAP administration and/or repeated electroconvulsive shock (ECS). The main goal of this study was to uncover the miRNA-mediated molecular mechanisms underlying psychotic symptoms.

Methods
Firstly, a number of the mouse behavioral paradigms were tested in animals treated with MAP and ECS, including novel object recognition test (NORT), prepulse inhibition (PPI), and behavioral sensitization. Secondly, differentially expressed miRNAs in hippocampus of mice pre-treated with MAP and/or ECS were identified via a genome-wide mature miRNA PCR array quantification. Finally, the inversely expressed miRNAs after MAP and ECS intervention were selected as candidate for *in vivo* and *in vitro* functional experiments. Using the lenti-viral expression vectors to perform the transduction in the mouse hippocampus, candidate mature miRNAs were either knocked-in and over-expressed, or knocked-down and down-regulated, to test whether the miRNA would have behavioral effects in mice.

Results
Overexpression of miR-328 in bilateral hippocampi of mouse could further impair the PPI deficit and behavioral sensitization cause by pre-treated MAP. On the contrary, knocking-down of miR-328 could partially rescue the PPI deficit and decrease the behavioral sensitization. We also identified that alpha-secretase coding gene BACE1 and post-density 95 protein coding gene DLG4, both were reported to be associated with the regulation of expression of AMPA receptors in postsynaptic neurons, were targets of miR-328.

Discussion & Conclusion
Elucidation of the roles of miRNA in the therapeutic mechanism of ECT would bring new insights into the pathogenesis of psychotic disorders, and shed some light on the development of new therapeutic agents.