Targeting hippocampal dysfunction improves cognition in a schizophrenia model
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INTRODUCTION

Recent clinical studies using neuroimaging and preclinical models of schizophrenia indicate that aberrant hippocampal excitability may contribute to cognitive impairment and augment psychotic symptoms due to disinhibition of dopaminergic neurons.

Treatments with compounds targeting hippocampal overactivity to normalize this condition might improve hippocampal-dependent memory and reduce dopamine hyperactivation via functional pathways connecting the hippocampus and the ventral tegmental area.

Here, we tested this therapeutic approach to assess both cognitive impairment and a potential benefit on other symptoms of schizophrenia associated with dopamine dysregulation.

In a well-established ketamine model, we tested rats with the antiepileptic medication, levetiracetam, which mediates its effect by reducing neural overexcitability.

The rats were tested for their hippocampal-dependent memory performance on a radial maze task, and for their dopamine responsiveness with an amphetamine challenge.

Rats were treated with different doses of levetiracetam and tested on the radial arm maze with a 3-hr retention interval.

As expected, ketamine-exposed rats committed significantly more memory errors than saline-exposed rats under vehicle (0 mg/kg) baseline condition.

Treatment with levetiracetam at 10 mg/kg, however, significantly reduced the number of memory errors in the ketamine-exposed rats compared to when they were treated with vehicle (0 mg/kg).

DISCUSSION

The preclinical ketamine model of schizophrenia has been shown to recapitulate hippocampal hyperactivity seen in patients with the illness.

We showed that animals in this model have a corresponding impairment in hippocampal-dependent memory that could be restored with levetiracetam treatment. The same treatment also normalized amphetamine-induced locomotor hyperactivity.

Together, our findings indicate that levetiracetam may be useful for normalizing hippocampal activity in schizophrenia-related cognitive dysfunction, as well as moderating a symptom of schizophrenia due to dopaminergic dysfunction.

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