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Treatment with levetiracetam improves cognition in a ketamine rat model of schizophrenia

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ABSTRACT

Imbalance in neural excitation and inhibition is associated with behavioral dysfunction in individuals with schizophrenia and at risk for this illness. We examined whether targeting increased neural activity with the antiepileptic agent, levetiracetam, would benefit memory performance in a preclinical model of schizophrenia that has been shown to exhibit hyperactivity in the hippocampus. Adult rats exposed to ketamine subchronically during late adolescence showed impaired hippocampal-dependent memory performance. Treatment with levetiracetam dose-dependently improved memory performance of the ketamine-exposed rats. In contrast, the antipsychotic medication risperidone was not effective in this assessment. Levetiracetam remained effective when administered concurrently with risperidone, supporting potential viability of adjunctive therapy with levetiracetam to treat cognitive deficits in schizophrenia patients under concurrent antipsychotic therapy. In addition to its pro-cognitive effect, levetiracetam was also effective in attenuating amphetamine-induced augmentation of locomotor activity, compatible with the need for therapeutic treatment of positive symptoms in schizophrenia.

1. Introduction

Cognitive deficits strongly predict long-term functional disability in schizophrenia, but existing standard-of-care antipsychotic medications lack efficacy for improving cognition and functional outcomes in patients (Corigliano et al., 2014; Eastvold et al., 2007; Green, 1996; Green et al., 2004; Jahshan et al., 2010; Nuechterlein et al., 2014). Disturbance in the balance of neural excitation and inhibition (E/I) is recognized as possibly contributing to both psychotic and cognitive dysfunctions in schizophrenia (Foss-Feig et al., 2017; Krystal et al., 2017). For example, recent evidence from human neuroimaging studies points to heightened neural activity localized to the medial temporal lobe as a potential driver of pathophysiology in schizophrenia, exerting significant adverse effects on cognitive function (Medoff et al., 2001; Sanderson et al., 2012; Schobel et al., 2009, 2013; Tregellas et al., 2014; Zierhut et al., 2010). Specifically, the level of neural hyperactivity correlates with worse cognitive performance in patients (Tregellas et al., 2014), and the hyperactivity in a prodromal phase of illness predicts clinical progression to overt psychosis within two years (Schobel et al., 2009).

Preclinical animal models of schizophrenia have recapitulated key neurobehavioral features of the disease, including E/I imbalance in the neural circuits important for cognitive function. For example, higher metabolic basal activity and neuronal firing rates have been observed in adult animals exposed prenatally to the antimitotic compound methylazoxymethanol acetate or to the NMDA receptor antagonist ketamine during adolescence (Gill et al., 2011; Lodge and Grace, 2007; Schobel et al., 2013). Importantly, those same pharmacological induction protocols that produce changes in neural activity lead to cognitive dysfunction detected by behavioral assessments (Koh et al., 2016; Moore et al., 2006). In vitro slice recordings from such treated animals have also provided evidence for neuronal hyperactivity of principal neurons in the hippocampus that are partially normalized by diazepam administration (Sanderson et al., 2012). Thus, both preclinical and clinical data suggest that increased neural activity is a condition contributing to dysfunction in this illness.

We set out to investigate whether targeting neural overactivity with levetiracetam, an atypical antiepileptic agent that binds with high affinity to the synaptic vesicle 2A (SV2A) protein to regulate synaptic exocytosis and neurotransmitter release, would be effective at improving cognition in an animal model of schizophrenia that has been shown to exhibit heightened neural activity. Levetiracetam has already been evaluated in an animal model of impaired sensory gating, and was found to improve auditory gating in mice with schizophrenia-like gating deficits (Smucny et al., 2015). Low dose treatment with levetiracetam has also been found to improve memory in aging and Alzheimer's disease that

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are associated with increased neural activity in the medial temporal lobe (Devi and Ohno, 2013; Hall et al., 2015; Koh et al., 2010; Sanchez et al., 2012; Suberbielle et al., 2013). Taken together, the beneficial effects of levetiracetam on normalizing neural overactivity suggests that reduction in neural overactivity by levetiracetam may have potential efficacy on cognition in schizophrenia.

In the present studies, we assessed the ability of levetiracetam to alleviate memory impairment in a ketamine animal model of schizophrenia that recapitulates neural hyperactivity and memory problems akin to those seen in schizophrenia patients (Koh et al., 2016; Olney et al., 1999; Neill et al., 2010; Schobel et al., 2013). We tested levetiracetam, alongside and in combination with the antipsychotic medication, risperidone, to compare their efficacy to improve cognition under the same testing conditions. We further examined whether levetiracetam alleviates the augmented response to a dopamine agonist amphetamine, a commonly used behavioral assay to assess a dopaminergic perturbation that is central to the illness. Levetiracetam, but not risperidone, was found to improve memory performance dose-dependently in a hippocampal-dependent memory task, and levetiracetam remained effective when administered concurrently with antipsychotic drug treatment. In addition, levetiracetam attenuated the response to amphetamine in the ketamine model, also suggesting a potential link between hippocampal overactivity and dopamine system dysfunction as proposed by other investigators (Grace, 2012; Lodge and Grace, 2007).

2. Materials and methods

2.1. Subjects

Male Long-Evans rats were obtained at approximately 5 weeks old from Charles River Laboratories (Raleigh, NC), and housed individually at 25 °C and maintained on a 12-h light/dark cycle. Food (Purina autoclave laboratory rodent diet) and water were provided ad libitum unless otherwise noted. All procedures in the current investigations were approved by the Institutional Animal Care and Committee in accordance with the National Institutes of Health directive.

2.2. Ketamine exposure

Ketamine (VedCo; 100 mg/ml concentration) was diluted in saline to 30 mg/ml, and injected at a volume of 1 ml/kg of body weight (Enomoto and Floresco, 2009). Rats were injected intraperitoneally twice daily (morning and late afternoon) with saline or ketamine (30 mg/kg) for two weeks starting at 7-weeks of age. Following ketamine exposure, the rats were left undisturbed for at least five days for drug washout before behavioral training.

2.3. Drug treatments

Levetiracetam (synthesized by Tecoland Corporation, Irvine, CA) and risperidone (Sigma, Saint Louis, MO) were tested for their effect on cognition. Levetiracetam was diluted in saline and dosed at 1, 5, and 10 mg/kg, and risperidone was diluted in a vehicle consisting of 0.25% Tween-80 in saline and dosed at 0.1, 0.17, and 0.3 mg/kg. The drugs were administered in a volume of 1 ml/kg intraperitoneally 30–40 min prior to test sessions. Levetiracetam doses were chosen based on their efficacy in targeting neural overactivity in rodents (Haberman et al., 2017; Koh et al., 2010), and risperidone doses were chosen based on antipsychotic clinical relevance (50% D_2 receptor occupancy and efficacy in animal models of antipsychotic activity; Wadenberg et al., 2001).

2.4. Overview of experiments

A set of ketamine-exposed rats (n = 23) was first tested on a radial arm maze task to assess memory impairment compare to control rats (n = 14). About half of these ketamine rats were then tested with risperidone (n = 11) and the remaining with risperidone-levetiracetam combination (n = 12) on the maze. The entire assessment on the radial arm maze took about 2 months to complete. A different set of ketamine-exposed rats (n = 14) was tested on the radial arm maze under levetiracetam treatment. A subset of these rats (n = 12) was then used to assess the efficacy of levetiracetam in the amphetamine-induced locomotor activity study together with a set of untreated controls (n = 7). The radial arm maze and amphetamine studies took approximately 2.5 months to complete.

2.5. Radial arm maze

A hippocampal-dependent radial arm maze task was used to assess the effect of drug treatment as described in detail elsewhere (Chappell et al., 1998; Koh et al., 2010). The protocol allowed repeated within-subject assessment at different drug doses and in combinations. Pretraining consisted of habituation, standard win-shift training, and win-shift training with delays interposed between information and memory test phases on the eight-arm maze. Drug treatments began a day after the completion of pretraining. Three arms were blocked at the beginning of each test trial (information phase). The identity and configuration of the blocked arms were varied across trials. Food-deprived rats were allowed to retrieve food reward (Kellogg's Froot Loops cereal) from the five unblocked arms. The rat was then removed from the maze for a retention interval, during which time the barriers on the blocked arms were removed allowing access to all eight arms. Rats were then placed back onto the center platform and allowed to retrieve the remaining food rewards (memory phase). An error consisted of returning to an arm (all four paws on the arm) from which food had already been obtained. The number of errors made in the retention phase was used to assess memory performance. We used a 3-h retention interval between information and memory test phases in all our drug studies based on our background data showing a reliable difference in memory performance between ketamine-exposed and saline control rats at that retention delay. Rats were tested with a series of drug doses in ascending/descending order; each dose, including vehicle alone, was thus tested twice.

2.6. Amphetamine-induced locomotor activity

Rats were challenged with amphetamine to examine dopamine-mediated hyperlocomotor activity and to determine whether levetiracetam treatment would alleviate the increased response to amphetamine that is characteristic of the ketamine model. Using a within-subject design, each rat was treated with either levetiracetam or saline on different test sessions; the order of drug treatment was counterbalanced such that half of the rats received levetiracetam on the first test session and saline on the second one, and vice versa. The test sessions were separated by at least one day of drug washout. During the test, each rat was injected intraperitoneally with levetiracetam (10 mg/kg) or saline and placed in an open field chamber (42 cm × 42 cm × 30.5 cm) in which locomotion was tracked with the VersaMax animal activity monitoring system (AccuScan Instruments, Columbus, OH). After 30 min of baseline activity, the rat was taken out of the chamber and injected intraperitoneally with a small dose of amphetamine (0.5 mg/kg in a volume of 1 ml/kg; Sigma, Saint Louis, MO). The rat was then returned to the chamber for another 60 min of activity monitoring. Total distance travelled and movement time were the dependent measures.

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