The novel antipsychotic Brexpiprazole partly reverses a disruption of thalamocortical function induced by phencyclidine

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Introduction

- There is a need for new treatments of schizophrenia as the currently prescribed classical and atypical, first and second generation, antipsychotics (antagonists of the dopamine D2 receptor and the serotonin 5-HT2A receptor, respectively) especially have failed to improve negative and cognitive symptoms.

- Brexpiprazole (BREX) is a promising novel antipsychotic drug of the third generation recently approved in the USA for the treatment of schizophrenia, with a different binding profile including a superior affinity for 5-HT2A and 5-HT2C adrenergic receptors. Yet the underlying mechanisms are still largely unknown.

- Non-compertitive NMDA receptor antagonists such as phencyclidine (PCP) are used as pharmacological tools to model schizophrenia. PCP disrupts thalamocortical function, increasing excitatory neuron firing and reducing low frequency oscillations (LFO; 0.5-4 Hz) in both the prefrontal cortex (PFC) and the centromedial (CM) and mediodorsal (MD) nuclei of the rostral thalamus.2 We have previously shown that various first and second generation antipsychotics drugs reverse these effects.2

- We aim to clarify the neuronal circuits involved in the antipsychotic effects of BREX, using the PCP model of schizophrenia. Specifically, we investigated the ability of BREX to reverse a disruption of thalamocortical function induced by PCP.

Materials & Methods

- Subjects. Male Wistar rats of 150-160g, anesthetized with chloral hydrate (5 g).
- In vivo electrophysiology. Single neurons and local field potential (LFP) were recorded extracellularly in the medial PFC (mPFC) and in the centromedial and mediodorsal (CM/MD) nuclei of the thalamus to investigate the effects of BREX (0.5 mg/kg) or neuronal firing rate and low frequency oscillations (LFO; 0.5-10 Hz). Glutamatergic neurons of the CM/MD thalamic nuclei were identified by action potential characteristics and burst firing (SF; 3.51 ± 0.64-0.64; SF-1 to SF-2 mm). Pyramidal NMDA neurons were identified by antidromic stimulation via the dorsal raphe or ventral tegmental area (n = 3, 14, SF-0.7; 12-0.4 mm). Glass micropipettes filled with 2M sodium chloride and 0.2 M potassium stannous chloride were used for recording. After an anesthetic overdose; the recorded location was histologically verified.
- Drug administration. After a baseline 5-min period, PCP (0.25-5 mg/kg, i.v.) was administered. When PCP augmented firing rate was reversed completely, as evaluated by the SF-2 mm, the NMDA antagonist BREX (0.5 mg/kg, i.p.) was administered. Each of the 30 dosing conditions were repeated in 4 different experiments (i.e., 30 sessions total) with PCP and BREX administered on different days. Average changes in neuronal activity were analyzed statistically using a two-way repeated measures ANOVA followed by post-hoc Newman-Kuels tests. Statistical significance is indicated with *p < 0.05.

Results

- PCP increases firing rate while decreasing LFO in CM/MD thalamus and mPFC

- Reversal by BREX

- mPFC: BREX partly restores the PCP-induced LFO decrease, but not the increase in firing rate. At higher doses, BREX restores both

- mPFC: BREX reverses a PCP-induced decrease of theta oscillations (4-10 Hz)

- Effects of PCP are reversed by the antipsychotic clozapine

- BREX alone

- mPFC: BREX (0.5 mg/kg, i.v.) reverses a PCP-induced excitation of CM and MD neurons, while failing to reverse a LFO decrease at the same dose.

Conclusions

- Thalamus: BREX (0.5 mg/kg, i.v.) reverses a PCP-induced excitation of CM and MD neurons, while failing to reverse a LFO decrease at the same dose.

- mPFC: BREX (0.5 mg/kg, i.v.) partly reverses a PCP-induced LFO decrease, while failing to reverse neuronal excitation of pyramidal neurons. Yet at higher doses (2 mg/kg, i.v.), both firing rate and LFO are restored. In addition, a PCP-induced decrease in theta oscillations is reversed, an effect suggesting antipsychotic activity.

Overall, BREX partly antagonizes thalamocortical hyperactivity associated with schizophrenia, with a stronger effect in the CM/MD thalamus, indicating a primary action in this area. These data provide more insight in the antipsychotic mechanisms of the novel drug Brexpiprazole (BREX).

References


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