The Role of KCNQ Potassium Channel in PCP mediated cognitive deficits

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INTRODUCTION

Schizophrenia is a chronic mental disorder that affects about 1% of the world population. In the U.S., there are more than 2.4 million individuals who suffer from this disease. Despite intensive research over the past 50 years, the neurobiological mechanisms and pathologies leading to schizophrenia are not well understood. As a result, there is no cure, and effective treatments for the disease symptoms are not available. We have identified the KCNQ (Kv7) potassium channels as a potential molecular target for the development of pharmacotherapies for schizophrenia. KCNQ potassium channels are slow-activating, slow-deactivating, voltage-dependent potassium channels that play a significant role in regulation of neuronal excitability and neurotransmitter release. These ion channels are widely distributed in the brain, including in regions implicated in pathologies of schizophrenia, such as the prefrontal cortex, hippocampus, and nucleus accumbens. The data from our laboratory suggests that modulation of KCNQ potassium channel function may be exploited for the treatment of behavioral symptoms of schizophrenia. The studies described here examine the role of KCNQ potassium channel blockers in modulation of behavioral deficits observed in the phencyclidine (PCP) animal model of schizophrenia.

METHODS

Materials and Methods

Animals: Male Sprague-Dawley rats weighing 300-450 grams were used for these experiments (Harlan Laboratories). Rats were individually housed in standard rat cages (lights on at 7:00 A.M., food and water available ad libitum). All experiments were conducted during the light cycle.

Prepulse inhibition: Rats were placed into chambers and exposed to a weaker stimulus (pulse) which typically leads to an inhibited reaction to a stronger stimulus (paw). This experiment tests sensorimotor gating, which is disrupted in schizophrenic patients.

T-Maze Paradigm: The rats were habituated to the animal facility for 4 weeks before testing and training began. These rats had no prior exposure to the food reward (Apple Jacks®) nor the T-Maze apparatus. The animals were then habituated to an empty maze for three days (10 minutes). After empty habituation, the rats were then forced to perform the maze in a forced alternating session (20 trials/day, 5 days). Following forced alternation, the rats were then run forodorance trials. In this stage, the rat is forced to one side (picked at random), allowed to eat the reward, then is returned to the “home” area (3 second delay) and then is permitted to an unobstructed maze in order to identify that the reward is present on opposite side as in the Forced Trial (20 seconds between individual trials).

Drugs: All drugs were obtained commercially. The phencyclidine (PCP) was obtained from The National Institutes of Health and dissolved in saline. DMP543 was dissolved in 40% DMSO in saline. The PCP was administered at 1.5 mg/kg (Sub-Q) and the DMP543 at 0.15 mg/kg (Sub-Q).

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CONCLUSIONS

KCNQ potassium channels play an important role in regulation of memory, attention, cognition, and social behavior.

Blockade of KCNQ potassium channel blockers reverses cognitive deficits and negative symptoms in animal models of schizophrenia.

Blockade of KCNQ potassium channels does not alter anxiety level as seen in the elevated plus maze model.

This data strongly suggests that KCNQ potassium channel blockers may be used for treatment of cognitive and negative symptoms of schizophrenia.

When using combined injections, the improvements in behavior is not increased as much as separate injections because DMP requires 45 minutes to act optimally.

FUTURE RESEARCH DIRECTIONS

Examine the possibility that pathophysiological activation of KCNQ potassium channel blocks cause cognitive and negative symptoms.

Characterize and optimize drug-like properties of KCNQ channel blockers.

Determine mechanism of action of KCNQ channel blockers on cognition and negative symptoms.

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Discrimination Index of different drugs administered

KCNQ (Kv7) potassium channels

Blockade of KCNQ potassium channels in the prefrontal cortex reverses deficits in forced delayed alternation

Prepulse inhibition is restored by DMP543