# The Role of KCNQ Potassium Channel in PCP mediated cognitive deficits

Aisha Bano, Tayaba Ahmad, M. Behnam Ghasezmadeh
Department of Biomedical Sciences, Integrative Neuroscience Research Center, Marquette University, Milwaukee, WI

## 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.

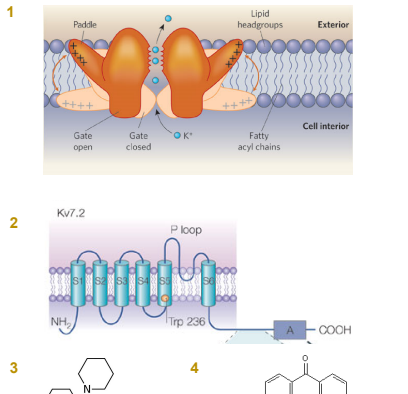
***Prepulse inhibition:*** Rats were placed into chambers and exposed to a weaker stimulus (prepulse) which typically leads to an inhibited reaction to a stronger stimulus (pulse). This experiment tests sensorimotor gating, which is disrupted in schizophrenic patients.

***T-Maze Paradigm:*** The rats were habituated to the animal facility for a number of 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 fashion (20 trials/ day, 5 days). Following forced alternation, the rats were then ran forced/choice 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 rounds).

***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 DMP453 at 0.15 mg/kg (Sub-Q).

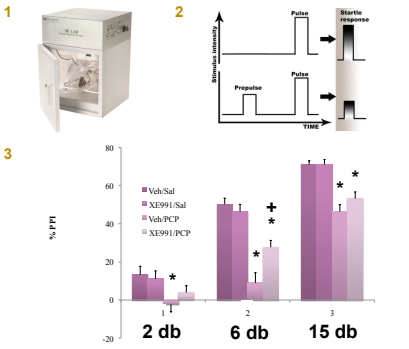
**This research was supported by Ronald McNair Program**

## KCNQ (Kv7) potassium channels



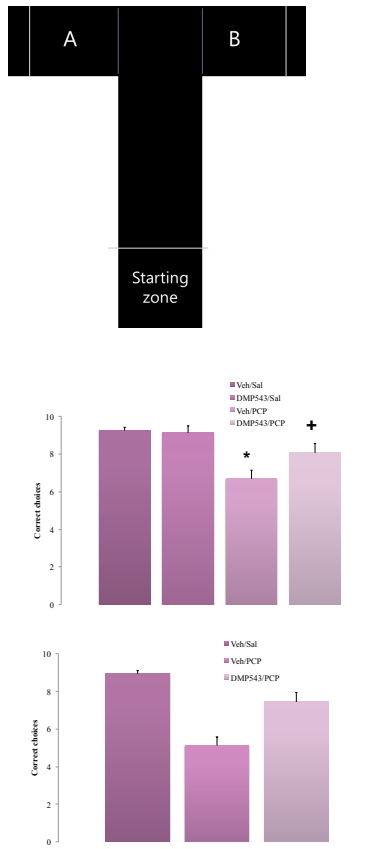

1: Schematic showing neuronal potassium channels; 2: Diagram showing structure of KCNQ potassium channels; 3: The chemical structure of phencyclidine (PCP); 4: The chemical structures of DMP543.

## Prepulse inhibition is restored by DMP543



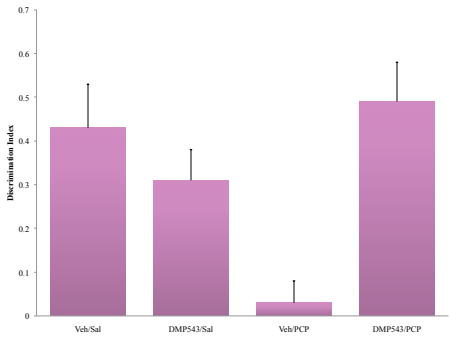

1: Rats are placed into plastic restraints inside prepulse inhibition chamber. The restraints record how much the rats jump; 2: Diagram depicting startle response with and without prepulse inhibition; 3: Animals were treated as shown in graph legend. PCP (1.5 mg/kg, sc) and XE991 (0.5 mg/kg, sc) were administered 15 minutes before session. XE991/PCP was administered as a drug cocktail 15 minutes before behavior. Percent of prepulse inhibition was recorded at 2, 6, and 15 db.

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




1: Diagram of the forced delayed alternation arena (T-maze). Rats are initially placed in starting zone. They are forced to enter either arm A or B. On the following trial, they are allowed to choose either arm. However, the food reward can only be found in the non-forced arm. Ten trials were performed by each rat. (n=16); 2: Rats were treated as shown, using systemic injections. DMP543 (0.15 mg/kg, sc) was administered 45 minutes before behavioral session. PCP (1.5 mg/kg, sc) was given 15 minutes prior to behavioral session. 3: Rats were treated as shown, using systemic injections. DMP543 (0.15 mg/kg, sc) and PCP (1.5 mg/kg, sc) combined were administered 15 minutes prior to behavioral session.

## Discrimination Index of different drugs administered




## CONCLUSIONS

- KCNQ potassium channels play an important role in regulation of memory, attention, cognition, and social behavior.
- Blockade of KCNQ potassium channels 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 sepeated injections because DMP requires 45 minutes to act optimally.

## FUTURE RESEARCH DIRECTIONS

- Examine the possibility that pathological activation of KCNQ potassium channels leads to 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.