

# **The Role of KCNQ Potassium Channel in PCP mediated Cognitive Deficits**

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# Introduction

- Schizophrenia -- splitting of the mind -- is a condition with severe psychopathology with three facets:
  - Positive symptoms, negative symptoms, and cognitive deficits
- Span: life-long but quality of life may improve later on
- Symptoms are observed in teen years

- Positive Symptoms
  - Hallucinations
  - delusions
  - thought disorders
  - Paranoia
- Treatments: anti-psychotic drugs targeting the dopamine system
  - Ineffective because of the side effects serving as deterrents.
  - Somewhat treatable because we understand the starting biochemical point – dopamine system – which manifests itself in the behavior.

- Negative Symptoms and Cognitive deficits
  - Once believed to be combined
  - Negative symptoms
    - Anhedonia
    - Social withdrawal
    - Thought poverty
  - Cognitive deficits
    - Poor attention
    - Impaired working memory
    - Impaired executive function.
  - Treatment: none because the starting biochemical point is unknown

# Proposition

- A very specific potassium channel in the brain needs to be blocked
  - This would restore the capacity to reach action potential
  - Potentially restore neurons functionality
  - This potassium channel is blocked by Dimethyltryptamine (DMP)

# Experiments – T-Maze

- The Tmaze Apparatus
  - Animals are forced to into one arm of the apparatus to eat the delectable apple jack
    - Done by blocking the other arm
  - Animals then are to make a decision to go in the other arm for food with no arms being blocked
  - This tests their learning memory and ability to make decision.
  - Rats with 90% or above accuracy undergo testing with PCP, DMP, and Retigabine.

# What is PCP, DMP, and Retigabine?

- PCP
  - A drug which targets the NMDA Receptors and induces schizophrenia like behavior
- DMP
  - DMP is a potassium channel blocker
    - Membrane potential can depolarize to  $\sim -70\text{mV}$  so action potential can occur
    - restore normal brain activity
    - significantly reverse the negative symptoms and cognitive deficits
- PCP
  - The opposite of DMP
  - potassium channel opener
    - further repolarizes the membrane potential preventing from action potential from occurring.

# Pre-Pulse Inhibition

- Schizophrenic patient suffers pre-pulse inhibition
  - Ability to recognize and remember a startling action when occurred repeatedly
  - Same startling response each time – hence the pre-pulse is inhibited
- Rats are divided into four groups
  - Control group: Vehicle/Saline
  - Experimental groups: PCP, DMP/PCP, Retigabine/PCP



# Expected Results

- Control experiment with Vehicle/Saline should not impact performance
- PCP should drastically decrease the performance roughly to 50% because their decision making is impacted and pre-pulse is inhibited
- DMP/PCP should significantly reverse the deficits induced by PCP by blocking the potassium channel allowing proper action potential to occur
- DMP/Retigabine should worsen the effect because it is further preventing action potential from being reached by opening the potassium channel causing deeper repolarization

- Results

- As expected
- Combined shots don't provide same level of effectiveness