The Role of KCNQ Potassium Channel in PCP mediated Cognitive Deficits

By: Aisha Bano
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 deterents.
  ◦ 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 ~-70mV 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