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Introduction

Schizophrenia, a neurodevelopmental disease, has "afflicted humans since the beginning of written history." The afflicted patients were often times perceived to be prophets or seers and other times to be manifestations of the devil (Tamminga & Holcomb, 2005). In the 15th century, it was believed that cutting certain nerves in the brain could eliminate excess emotion and stabilize a personality of the mentally ill, so lobotomy – a form of psychosurgergy – was practiced (Tartakovsky, 2011). It was not until the late 19th century that compassionate treatment for these patients surfaced. Schizophrenia, which literally means splitting of the mind, has severe psychopathology with three facets: positive symptoms, negative symptoms, and cognitive deficits. The present understanding of schizophrenia is one which, describes patients in terms of their psychopathology, impairment of function and ability to sustain a normal life style and role in society. The severity and experiences range from person to person: one individual may experience a single episode and continue with his or her life, whereas the majority, however, will experience multiple relapses with autonomous functions in between and will need medications and support. Unfortunately, the course of schizophrenia is life-long and often times, the disease may have a rather fast onset and symptoms initially showing in late teens and early adult years (Tamminga & Holcomb, 2005). Schizophrenia is observed in 1% of the general population but other factors can contribute to increase the risk of schizophrenia.

Positive Symptoms

Positive symptoms present an excess or distortion of normal functions; the main symptoms include delusions, hallucinations, thought disorder and disorganized behavior.

Delusions are simply beliefs and convictions which, are not based on reality, and they are a result of misinterpreting perceptions and experiences and this is the most common schizophrenic symptom. In hallucinations, these patient claim to hear sounds and see things that do not exist, and hearing sounds is the most common form of hallucination among schizophrenics. Thought disorder refers to the difficulty in schizophrenic patient to organize thoughts and speaking. He or she may often times stop midsentence to collect his thought process. And disorganized behavior alludes to simple childlike silliness to intense agitation (Mayo Clinic, 2012).

Negative Symptoms

Negative symptoms are the critical features of schizophrenia and they highlight an absence of normal mental functions; they consist of affective flattening (lack of emotional expression), alogia (lack of logic), avolition (inability to utilize free will), anhedonia (inability to feel pleasure), and attention impairment (Wyss, et al., 2013).

Negative symptoms often cause social impairment which translates into low success rate in social and professional life and this explains much of the long-term morbidity and poor functional outcomes of those afflicted with

schizophrenia impairment (Wyss, et al., 2013). Much evidence has been accumulated over time to support that negative symptoms is a facet of its own in schizophrenia (Blanchard & Cohen, 2006).

Cognitive Deficit

The third facet of schizophrenia is cognitive deficits, which previously was clustered with negative symptoms, but with recent clinical studies, it is now highlighted as a third major diagnostic category of schizophrenia. Furthermore, it is also considered to be the core deficit of the disorder (Castner, et al., 2004). Cognitive dysfunction includes but is not limited to working memory defects, attention dysfunction, verbal and visual learning and memory, processing speed and social learning (Tamminga & Holcomb, 2005). The severity of cognitive dysfunction is the best predictor of "social functioning, unemployment and even relapse" (Castner, et al., 2004).

Since working memory is vital for "integrity of thought process," it can be concluded that malfunction of the neural circuitry of working memory may be the underlying cause of cognitive deficits and associated thought disorders in schizophrenia (Castner, et al., 2004). Functions that are associated with frontal cortex are abnormal (i.e., verbal fluency, spatial performance, and pattern recognition) and long-term memory is affected (Tamminga & Holcomb, 2005). Additionally, schizophrenic patients perform poorly on tasks which, required vigilance or paying attention, and these are particularly associated with the anterior cingulated (Tamminga & Holcomb, 2005). Furthermore, deficits due to

malfunctioning of the hippocampus may occur, affecting explicit memory, verbal memory and working memory. An impacted working memory can justify the lack of organization in thought processes because the ability to hold information "on-line" is rather crucial for the organization of future thoughts and even associating them with recent past (Tamminga & Holcomb, 2005).

Treatments

Treatment of schizophrenia has evolved over the centuries: in 15th century, schizophrenic were considered to be evil and possessed and were treated with lobotomy; however, as time went on, it was discovered that they were mentally ill (Tamminga & Holcomb, 2005). In early 1930, they were treated with unusual and unlikely methods such as fever therapies, adrenalectomy, and vasectomy; these were all based on pure speculations. Towards the end of World War II, with the overwhelming necessity for treatment, Reserpine was administered with some improvement but it also came with significant side effect. Chlorpromazine, however, was the first effective and selective antipsychotic drug and it was discovered by "clinical serendipity" (Tamminga & Holcomb, 2005).

The discovery that chlorpromazine and other phenothiazines showed dramatic effects in control of psychosis which led to the convening of the American College of Neuropsychopharmacology (ACNP) (Moghaddam & Javitt, 2012). Implementation of these treatments allowed many patients to be deinstitutionalized and to carry on with their daily lives (Tamminga & Holcomb, 2005). Shortly thereafter, a linkage between antipsychotic drugs and blockade of

D2-Type dopamine receptor was found which allowed for the production of the drugs, phenothaizine and non-phenothiazines. Fifty years later, the primary treatment for schizophrenia remains practically unchanged: clozapine, (developed in 1961), is the most efficacious drug. There have been numerous attempts to mimic a drug of the same result without its “hematological and orthostatic side effects” and failures normally observed in negative symptoms and cognitive deficits (Moghaddam & Javitt, 2012). There is not a consensus on one particular antipsychotic which can sufficiently treat debilitating cognitive dysfunction due to schizophrenia (Castner, et al., 2004); however, a realization which has been unanimously reached is that, “not only are we in need of alternative medications but [also] alternative targets” (Moghaddam & Javitt, 2012).

Genetics

The disease is characterized by the three facets – positive, negative and cognitive symptoms. Population, families and twin studies indicate that schizophrenia is “highly heritable”; however, no single gene can induce such effects. Rather, the disease is byproduct of synergistic interactions of various genes and environmental factors. With studies in the field of association and linkage, over dozens of risks genes for schizophrenia have been identified (Lisman, et al., 2008).

While genes play a significant role in development and occurrence of schizophrenia, research is also being conducted with a focus on neurotransmitter

systems and evidence continues to point abnormalities present in more than one system. One thing which is certain is that it is not one simple system that is malfunctioning and rather it is a combination of glutamate, GABA, dopamine and acetylcholine system malfunction that is contributing and giving rise to this disease (Lisman, et al., 2008).

This evidence essentially suggests the idea that there is a dire need to take an integrative approach towards schizophrenia that takes into the account the synergistic way those genes and neurotransmitters work to produce this illness (Lisman, et al., 2008).

Neurodevelopment

A schizophrenic brain is distinct from a typical brain and it has been considered a neurodevelopmental disorder for past 25 years. It can be drawn that aberrant development during fetal, childhood or adolescent periods can potentially account for these pathological changes. Further, the popular perspective is that the neurodevelopment changes can be explained by genetic predisposition, early adverse event such as “mid-gestational insults.” It is widely agreed that adolescence is a critical period but also that pre and perinatal development are susceptible time periods which, may contribute to onset of schizophrenia. Recent studies are showing that schizophrenia is not restricted to the womb but rather it is a process, which continues post-birth as well as in adolescence and early adulthood. This provides an opportunity for potential perturbation during these periods because it is believed that these periods

contribute to the onset of schizophrenia and therefore serve as critical timeframes to target (Catts, et al., 2013).

Prenatal period is a critical and sensitive time in which exposure in the uterus can impact the course of development and the offspring. For example, early immune system development gives rise to changes in the fetal immune system. There is evidence from epidemiological and genetic studies that suggest that immune dysregulation in the developing brain might play a role in the development of schizophrenia. (Marques, et al., 2013). The timing of immune dysregulation with “respect to gestational age and neurological development of fetus” creates a sensitive window of vulnerability which can be targeted (Marques, et al., 2013). The fetal immune system is particularly vulnerable to disruptions caused by environmental factors such as malnutrition, toxins, stress and anxiety (Marques, et al., 2013).

Impairments in the neurodevelopment translate into various cognitive domains such as verbal memory, processing speed and the other symptoms discussed previously.

KCNQ Potassium Channels

KCNQ potassium channels (Kv7) are voltage-dependent potassium channels “composed of homo- and hetero-tetrameric complexes of five different KCNQ subunits” – Kv7.1 – Kv7.5. All these subunits except Kv7.1 are strongly expressed in neuronal tissue including neocortex and hippocampus and “their activation is responsible for the generation of M current, an inhibitory K+ current

regulating repetitive action potential discharges" (Sotty, et al. 2009). There have been many attempts in the past to discover pharmacological KCNQ modulators as a method to treat the central nervous system diseases; retigabine was the first and it is a KCNQ potassium channel opener (Sotty, et al., 2009).

All subtypes of KCNQ channels start to open around -60 mV; they can also be considered as non-activating leaky K^+ channels at relevant resting potentials and a fraction of the may undergo steady-state inactivation. Given these characteristics, they are able to produce the "underlying subthreshold M-Current" which then can stabilize the neuronal resting potential. In turn, these are thought to inhibit excitability and essentially put action potential to halt upon the exposure to an excitatory stimulus (Hansen, et al., 2008).

Hypothesis

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

Animals

Male Sprague-Dawley rats from Harlan Laboratories weighing 300-450 grams were used for these experiments. Rats were individually housed in standard rat cages with 12/12 hrs light cycle with lights on at 7:00 A.M., food and water were available ad libitum. All experiments were conducted during the light cycle.

Prepulse inhibition

Rats were placed into chambers and exposed to a weak stimulus pulse of sound (2, 6, or 15 db prepulse), which typically inhibits startle reaction to a stronger stimulus (110 db pulse). This experiment tests sensorimotor gating, which is disrupted in schizophrenic patients.

Delayed-Alternation Working Memory Paradigm

The rats were habituated to the animal colony for about a week before training began. These rats had no prior exposure to the food reward (Apple Jacks) nor the T-Maze apparatus. Subsequently, animals were habituated to an empty maze for three days (10 minutes/day). After initial habituation, the rats were trained to perform in the maze in a forced, alternating fashion (20 trials/day for 5 days). Following forced alternation, rats were trained to perform in

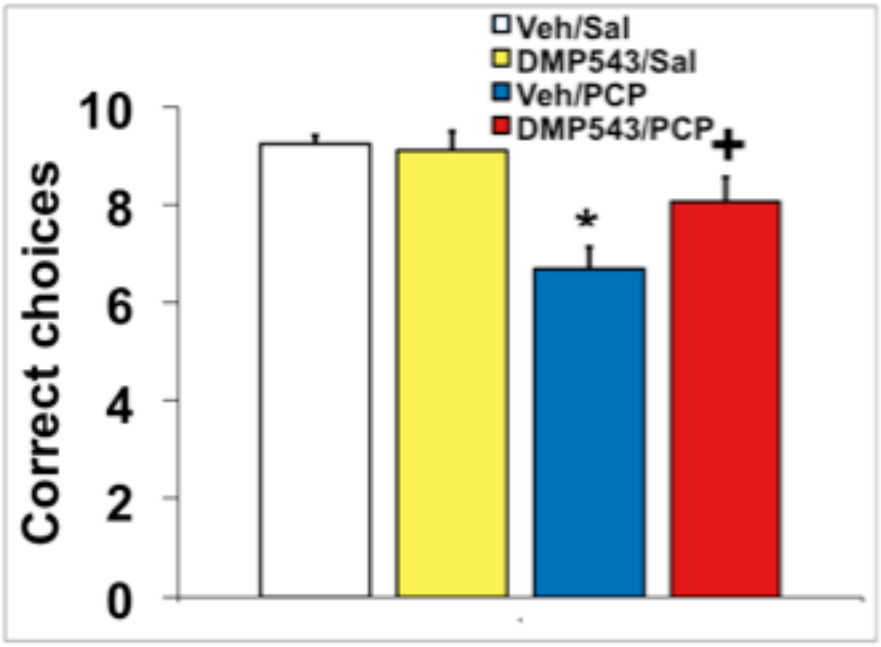
forced/choice trials. In this stage, the rat is forced to one side (picked at random), allowed to eat the reward, then is returned to the “home” area and following a 3 seconds delay is permitted to enter the unobstructed maze in order to identify that the reward is present in the opposite arm (20 seconds between individual rounds).

Drugs

The phencyclidine (PCP) was obtained from the National Institutes of Health and dissolved in saline. All other drugs were obtained commercially. DMP543 was dissolved in 40% DMSO in saline. The PCP was administered at 1.5 mg/kg, subcutaneously and the DMP453 at 0.15 mg/kg, subcutaneously.

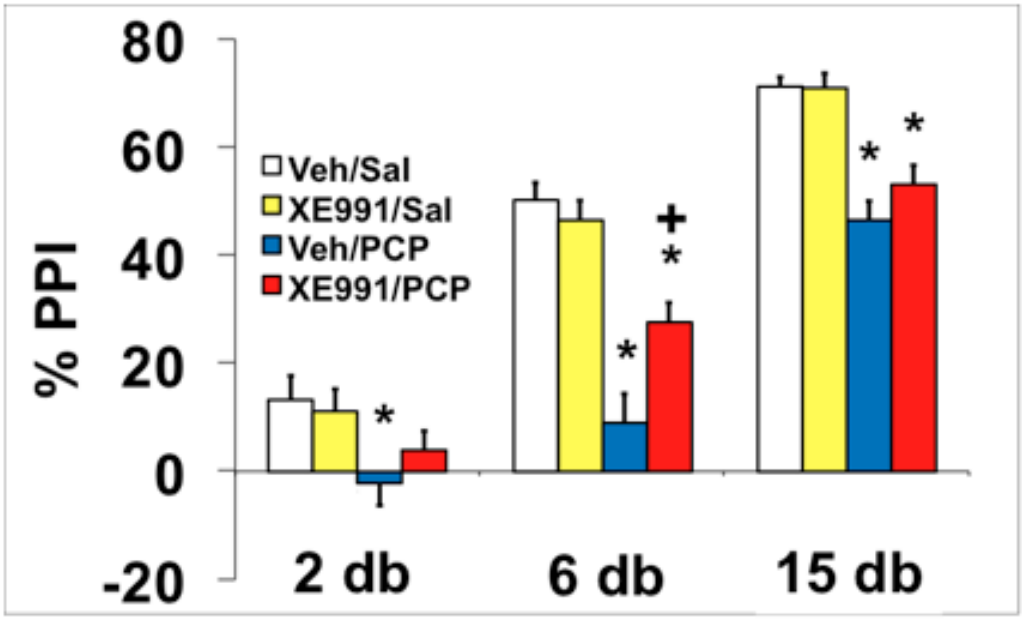
Results

Delayed-Alternation Memory Task



The data show that rats performed at about ≥90% accuracy when treated with Vehicle/Saline which, serves as control group. Animals injected with DMP543/Saline alone do not show any decrease in performance compared with the control group. However, when PCP is administered to these animals, there is a significant decrease in the performance roughly to 60-70%. But DMP543 can reverse the PCP effects on memory in these animals, an increase to ~85% is observed.

Prepulse Inhibition



This graph shows the percent prepulse inhibition recorded at prepulses of 2, 6, and 15 db. As clearly depicted by the graph, it shows when PCP is

administered, the prepulse inhibition is decreased significantly. However, when the KCNQ potassium channel blocker, XE991, is used, there is a significant improvement in the prepulse inhibition.

The results of these studies do in fact support our hypothesis that blocking the KCNQ potassium channel in the brain can reverse the detrimental effects of PCP on normal animal behaviors. A significant reversal is observed in these animals in their behavior including working memory and prepulse inhibition of startle response.

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