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A Comprehensive Review on Experimental Animal models to Induce Schizophrenia

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ABSTRACT

Schizophrenia is a mental illness that leads to alteration in perception, thinking and behavior. It often includes psychotic experiences, such as hearing voices or delusions. Developing reliable, predictive animal models for complex psychiatric disorders like schizophrenia, is vital to increase our understanding of the neurobiological basis of the disorder and for the development of novel drugs with improved therapeutic efficacy. Most rodent models have behavioral phenotype changes that resemble 'positive-like' symptoms of schizophrenia, probably reflecting altered mesolimbic dopamine function, but fewer models also show altered social interaction, learning and memory impairment, analogous to negative and cognitive symptoms of schizophrenia respectively. The present review aimed to presents the detail background about the symptoms, pathophysiology and treatment particularly focusing on various animal experimental models to induce Schizophrenia.

Key words: Cognitive, Dopamine hypothesis, Negative symptoms, Positive symptoms, Schizophrenia.

I. INTRODUCTION

Schizophrenia is a serious mental health issue that is characterized by disturbances in thought. Indian studies have suggested that the prevalence of schizophrenia is lower in India than in the West may be one of the reasons for this difference could be underreporting. The prevalence of schizophrenia in "least developed" countries was significantly lower than in the "emerging" and "developed" countries (Biju Viswanath et al., 2015). Incidence of schizophrenia is high which accounts for almost 1 in every 276 people 1 or precisely 2.5 million people, throughout the world today (Hafner et al., 2014).

The symptoms of schizophrenia fall into three broad categories: positive, negative and cognitive symptoms. **Positive symptoms** are psychotic behaviors not seen in healthy people.

People with positive symptoms often lack in-sight with reality. Sometimes they are severe and at other times hardly noticeable, depending on whether the individual is receiving treatment (Schizophrenia booklet, NIMH 2009). Sometimes hallucinations, delusions, catatonic behavior, disorganized speech and thought disorders may also observed. **Negative symptoms** are associated with disruptions to normal emotions and behaviors. These symptoms are harder to recognize as part of the disorder and can be mistaken for depression or other conditions (Schizophrenia booklet, NIMH 2009). These symptoms include flat affect, lack of pleasure in everyday life, lack of ability to begin and sustain planned activities and lack of social interaction. **Cognitive symptoms** are faint. Like negative symptoms, cognitive symptoms may be difficult to recognize as part of the disorder (Schizophrenia booklet, NIMH 2009). Often, they are detected only when other tests are performed and these include poor executive functioning, trouble focusing or paying attention and problems with working memory.

2. PATHOPHYSIOLOGY

Pathophysiology of schizophrenia remain unclear but numerous evidences suggest that alterations in several neurotransmitters systems like Dopamine, Glutamate, GABAergic, serotonin are involved in the pathophysiological processes leading to the expression of the symptoms. Among these, the dopamine system has received most attention.

Genes and environment: Scientists have long known that schizophrenia runs in families. The illness occurs in 1 percent of the general population, but it occurs in 10 percent of people who have a first-degree relative with the disorder, such as a parent, brother, or sister. People who have second-degree relatives with the disease also develop schizophrenia more often than the general population. The risk is highest for an identical twin of a person with schizophrenia (Schizophrenia booklet, 2009).

2.1. Dopamine Hypothesis

- Dopamine and dopaminergic mechanisms play a central role in pathophysiology of Schizophrenia where the Dopamine hypothesis is one of the most established hypotheses.
- Van Rossum in 1966 proposed the First DA hypothesis of Schizophrenia i.e. Hyperactivity of DA transmission was responsible for this disorder (Wen-Jun Gao., 2011)
- This hypothesis was established based upon the observations that psycho-stimulants that increase DA levels can activate DA receptors and causes psychosis whereas antipsychotic drugs can treat psychosis by blocking dopamine D2 receptors.
- Together these further studies led to the another hypothesis that , decrease in DA transmission at D1 receptors in the prefrontal cortex might be implicated in the cognitive impairment and negative symptoms of Schizophrenia whereas excessive DA transmission in striatum may cause positive symptoms (Gordana Rubesa et al., 2011).
- However, if abnormal DA neurotransmitter functions were totally responsible for the pathogenesis of Schizophrenia , antipsychotic drugs could have provide anabsolute cure

for Schizophrenia – rather than being partially effective for most or ineffective in some of the cases.

- Although the DA hypothesis remains insufficient to clearly explain the complexity of this devastating disorder it offers a direct relationship to symptoms, particularly positive symptoms and to their treatment.

2.2. Glutamate Hypothesis:

For decades Schizophrenia research had been focused on the Dopamine hypothesis of Schizophrenia which states that dopaminergic neurotransmission abnormality plays a major in pathophysiology. Although numerous studies point to Dopaminergic abnormalities in Schizophrenia, Dopaminergic dysfunction cannot account for all the symptoms seen in Schizophrenia. Now numerous studies have focused on Glutamate hypothesis were the hypo functioning of Glutamate activity also leads to Schizophrenia (Maria D.Rubio et al., 2012)

- Glutamate is the principal excitatory neurotransmitter in CNS that can excite and activates any CNS neuron. It is an amino acid, employed as a building block in protein biosynthesis
- Cortex – brain stem cortical projections communicate with mesolimbic dopaminergic pathway through GABA interneurons in ventral tegmental area (VTA). Excitatory glutamate stimulation of interneuron NMDA receptors causes the release of GABA that usually mediates the inhibition of dopamine release in mesolimbic dopamine pathway.
- Therefore, the descending glutaminergic pathway under normal circumstances acts as a brake in mesolimbic dopaminergic pathway. If the NMDA receptor residing on GABA interneurons becomes hypoactive, no descending effect of tonic inhibition will occur, the net result being hyperactivity of the described dopaminergic pathway.
- These are the outlines of the theory for the biology of mesolimbic dopamine hyperactivity that is linked to the positive symptoms of psychosis.
- The cortex – brain stem projection communicates directly with the mesocortical dopaminergic pathway in VTA (therefore, there are no GABA interneurons here), and causes tonic excitation in normal circumstances (i.e., it acts as an accelerator of mesocortical dopamine neurons).
- If the NMDA receptors in the cortex – brain stem projection become hypoactive, the tonic excitation is lost, and mesocortical dopaminergic pathway becomes hypoactive, potentially offering an explanation for cognitive, negative and affective symptoms of SCH
- Hypofunction of NMDA receptors within five glutamate pathways may potentially account for positive, negative, affective and cognitive symptoms; also, it provides an explanation for deregulation of dopamine due to hypofunciton of NMDA receptors, resulting in hyperactivity in mesolymbic dopaminergic pathway for positive symptoms and hypoactivity in mesocortical dopaminergic pathway for cognitive, negative and affective symptoms of SCH (Coyle JT et al., 2006)

2.3. Serotonin hypothesis

Serotonin receptors are involved in psychomimetic and psychotogenic properties of hallucinogens.

- Recently, a lot of attention has been given to the abnormalities of serotonin system that might be connected with the development of SCH. The discovery that hallucinogen agents like indolamine and phenetilamine that exert their actions on CNS via 5HT2 receptors, a conclusion has been made that the hallucinations in SCH might occur through similar mechanism.

The following observations have been made in Schizophrenic patients

a) There is an increase in number of cortical 5-HT_{2A} and 5-HT_{1A} receptors in the brain of schizophrenic patients
b) 5- HT_{2A} and 5-HT_{1A} receptors have major role in the onset and treatment of side-effects of atypical antipsychotics.
c) 5-HT_{2A} receptor mediated activation of prefrontal cortex may be insufficient in schizophrenic patients. (Aghajanian GK et al.,2000).

3. TREATMENT

Because the causes of schizophrenia are still unknown, treatments focus on eliminating the symptoms of the disease. Treatments include antipsychotic medications and various psychosocial treatments. The pharmacotherapy of schizophrenia is represented in table-1 (HL Sharma, K.K. Sharma, 2013).

Table-1: represents antipsychotic drugs, mechanism of action (MOA), therapeutic use, adverse drug reaction (ADR).

S.No	DRUG	Category	Mechanism of action	THERAPUTIC USE	Adverse drug reaction
1	Chlorpromazine	Typical	D2 Receptor blocker	Psychiatric conditions, Huntington's disease	1. Extrapyramidal side effects, 2. Gyanaecomastia, 3. Agranulocytosis 4. Jaundice
2	Thioridazine	Typical	Partial dopamine receptor agonistc	positive or negative symptoms,	*Weight gain*
3	Clozapine	Atypical	5-HT2A, D1, D4, H1, α-Adrenergic, Muscarinic	Potent antipsychotic	Agranulocytosis Weight gain Hyperglycemia Epileptigenic

4	Fluphenazine	Typical	D2 Receptor blocker	paranoid psychoses	EPS
5	Haloperidol	Typical	D2 Receptor blocker	Acute SCZ Gilles de la Tourette's syndrome Huntington's disease	CNSdepression; QTc interval prolongation
6	Aripiprazole	Atypical	Partial agonist at D2 and 5-HT1A and agonist at 5-HT2A	SCZ, Mania Bipolar disorder	Tachycardia Dyspepsia Hypothyroidism
7	Chlorpromazine	Typical	Blocks D2 receptors	Autism, schizophrenia.	
8	Iloperidone	SDA	D2 and 5-HT2A receptor antagonist		
9	Loxapine	-	Dopamine blocker,exactly unknown	Schizophrenia and other psychotic disorders	-
10	Olanzapine	Atypical	5-HT2A, D1, D4, H1, α-Adrenergic, Muscarinic	Mania Schizoaffective disorders Tourette's syndrome	Weight gain Hyperglycemia Anticholinergic side effects
11	Quetiapine	"	"	"	Weight gain Hypotension Drowsiness
12	Risperidone	"	5-HT2A, D2, H1, α-Adrenergic	Effective against positive and negative symptoms	Anorexia Agitation Drowsiness
13	Sertindole	SDA		Acute and chronic schizophrenia.	Phaeochromocytoma
14	Thioridazine	Typical	D2 antagonist, prominent anticholinergic property	Positive symptoms	Retinal degeneration Lenticular opacities.
15	Ziprasidone	Atypical	5-HT2A, 5-HT2C, 5-HT2D etc,.	Antidepressant Anxiolytic Antipsychotic	Sedation Hypotension Arrythmogenic drug

3.1. Psychosocial treatments (Schizophrenia booklet.,2009):

- Psychosocial treatments can help people with schizophrenia that is already stabilized on antipsychotic medication. Psychosocial treatments help these patients deal with the everyday challenges of the illness, such as difficulty with communication, self-care, work, and forming and keeping relationships.
- Patients who receive regular psychosocial treatment also are more likely to keep taking their medication, and they are less likely to have relapses or be hospitalized. A therapist can help patients better understand and adjust to living with schizophrenia.
- The therapist can provide education about the disorder, common symptoms or problems patients may experience, and the importance of staying on medications.

3.2. Illness management skills:

People with schizophrenia can take an active role in managing their own illness. Once patients learn basic facts about schizophrenia and its treatment, they can make informed decisions about their care. If they know how to watch for the early warning signs of relapse and make a plan to respond, patients can learn to prevent relapses. Patients can also use coping skills to deal with persistent symptoms.

3.3. Rehabilitation:

Rehabilitation emphasizes social and vocational training to help people with schizophrenia function better in their communities. Because schizophrenia usually develops in people during the critical career-forming years of life and because the disease makes normal thinking and functioning difficult, most patients do not receive training in the skills needed for a job.

Rehabilitation programs can include job counseling and training, money management counseling, help in learning to use public transportation, and opportunities to practice communication skills. Rehabilitation programs work well whento improve cognitive or thinking skills. Programs like this help patients hold jobs, remember important details, and improve their functioning.

3.4. Family education:

People with schizophrenia are often discharged from the hospital into the care of their families. So it is important that family members know as much as possible about the disease. With the help of a therapist, family members can learn coping strategies and problem-solving skills. In this way the family can help make sure their loved one sticks with treatment and stays on his or her medication. Families should learn where to find outpatient and family services.

3.5. Cognitive behavioral therapy:

Cognitive behavioral therapy (CBT) is a type of psychotherapy that focuses on thinking and behavior. CBT helps patients with symptoms that do not go away even when they take medication. The therapist teaches people with schizophrenia how to test the reality of their thoughts and perceptions, how to "not listen" to their voices, and how to manage their symptoms overall. CBT can help reduce the severity of symptoms and reduce the risk of relapse.

4. EXPERIMENTAL MODELS TO INDUCE PSYCHOSIS

4.1. Amphetamine induced Stereotype in Rats (Corbett R et al., 1995):

Amphetamine is an indirect sympathomimetic agent. It induces licking, gnawing, grooming, sniffing (stereotype) in Rats which can be successfully prevented by classical neuroleptic agents. This test is predictive of antipsychotic drug, for D2 receptor antagonism.

Animals: Adult Wistar rats
Body Weight: 180-220 g
Inducing agent: d-Amphetamine
Standard drug: Haloperidol
Dose of I.A: 5 mg/kg
Route of administration: Intraperitoneal
Procedure:

1. Two groups (n=6) of adult Wistar rats were taken weighing between 180 to 220gm and were treated with either test or the standard drug (Haloperidol) and then placed in individual cages.
2. They were injected with d- amphetamine (5mg/kg ip) after 30 mins. The onset of stereotypic behavior was evaluated at 30 minutes interval for 3 hours. The reduction in mean stereotype score is indicative of antipsychotic effect.

4.2. Phencyclidine (PCP) Induced Bizarre pattern of locomotor activity (Rajiv Jash et al., 2013):

Phencyclidine is a glutamate receptor antagonist. Administration of phencyclidine has been found to induce locomotor hyperactivity in rodents and is antagonized by antipsychotic drugs.

Animals: Adult Wistar rats
Body Weight: 150-200 g
Inducing agent: Phencyclidine
Standard drug: Clozapine
Dose of I.A: 2 mg/kg
Route of administration: Oral
Procedure:

1. Animals were divided into groups (n=6), for test or the standard compound 30 minutes before the start of the experiment, the animals were administered with the extract or the standard drug.

2. Phencyclidine (2mg/kg) was administered to the animals of both the groups just before the start of the experiment. Then the locomotor activity of the animals will be measured in photoactometer for a session lasting for 90 mins.
3. Drugs antagonizing the phencyclidine induced activity are expected to act by some other receptor viz. Glutamatergic and Serotonergic rather than dopaminergic receptors.

4.3. Phencyclidine (PCP) Induced Social withdrawal test (Rajiv Jash et al., 2013)**:**

This test helps to show the effectiveness of potential antipsychotic drugs against negative symptoms of schizophrenia. Phencyclidine decreases the time of social interaction in the rats.

Animals: Adult Wistar rats
Body Weight: 150-200 g
Inducing agent: Phencyclidine
Standard drug: Clozapine
Dose of I.A: 2 mg/kg
Route of administration: Oral
Procedure:

1. Naïve Male Wistar rats were housed in pairs for 10 days prior to the start of the experiment. During the test one cage mate is removed and a new one is kept in the cage for 20 minutes.
2. The amount of social interaction is measured as the total amount of time spent on various elements of interaction i.e. social exploration, and genital investigation.
3. Phencyclidine will be administered 5 minutes before the start of the experiment whereas the test or the standard drug will be given 30 minutes before the experiment.

4.4. Conditioned Avoidance Response in rats (Apanna choudary et al., 2013):

1. Perhaps the oldest animal model to predict potential antipsychotic drug efficacy is the conditioned avoidance response (CAR). In the conditioned reinforcement model, experimental animals are trained to perform a certain response i.e. to avoid a mild shock.
2. Trained avoidance responses may be active (pressing a lever, climbing a pole, or jumping out of a box). Classical antipsychotic drugs reduce avoidance responding at doses that do not impair natural (untrained) escape.
3. Three groups of rats (each having twenty rats) weighing 150-250 Gms were tested in this model for test drug (2 doses) or standard.
4. 10 days of training period were carried out before the experiment, and a total of 20 sessions of training were imparted to each rat before the experiment. Test or the standard drugs were administered 30 mins before the start of the experiment.

4.5. Induction of catalepsy in Rats (Parle millind et al., 2013):

Animals: Adult Wistar rats
Body Weight: 180-200 g
Inducing agent: Phencyclidine
Standard drug: Clozapine
Dose of I.A: 2 mg/kg
Route of administration: Oral

Procedure

Rats are randomly divided in three groups (test or standard). After an appropriate pretreatment time of the drug, each rat is tested for with respect to the right and left front paws which are first put on columns, first 3 cm and then 9 cm high.

The cataleptic state was considered if the rat maintains the abnormal posture for 10 sec or more. The scoring was done according to the following

0- The rat moves normally when placed on a table.
1- Rats move only when touched or pushed.

1+1=2 – Rats placed on a table with front paws set alternately on a 3 cm high block fails to correct the posture in 10 secs, scored as 1 point for each paw, with a total of 2 for both paws.
1+1=2 – Rats placed on a table with front paws set alternately on a 9 cm high block fails to correct the posture in 10 secs, scored as 1 point for each paw, with a total of 2 for both paws.
This model predicts the extrapyramidal side effects of the test drug

4.6. Prepulse inhibition of the acoustic startle response (Das A et al., 2000):

1. Rats were left undisturbed for an acclimatization period of 10 days prior to testing.
2. All testing occurred over one day. PPI was measured in 4 startle chambers consisting each of a Plexiglas tubes mounted on a Plexiglas base within a sound-attenuating chamber. Chamber assignment was counterbalanced for prenatal treatment and chambers were cleaned with a 70% alcohol solution between animals.
3. A piezoelectric strain meter attached to the base transduced the startle response and was digitized and recorded by a computer. A speaker located in the ceiling of the sound attenuating chamber presented all acoustic stimuli and maintained a constant background noise level of 70 dB.
4. Startle reactivity was assessed by exposing animals to 40 ms, 120 dB acoustic stimulus alone. An average of fifty 1-ms readings, beginning at the onset of the startle stimulus, was used as the dependent variable. PPI of acoustic startle responses was measured by having the 120 dB startle stimulus proceeded by a 20 ms prepulse stimulus of 4, 8, 12, and 16 dB above background, which terminated 80 ms before the onset of the startle stimulus (prepulse-pulse trials).
5. The testing session consisted of 12 startle-only trials, 12 no-stimulus (null) trials, and 24 prepulse-pulse trials. Each session began with a 5 min acclimation period of background

noise. This was followed by trials arranged in pseudorandom order to prevent consecutive presentations of the same trial type.

6. The degree of PPI of acoustic startle response was calculated as a percentage for each prepulse intensity using the following formula:

100% X (1- (mean prepulse trial – mean null)/(mean startle – mean null)

Drugs. D-Amphetamine sulfate was dissolved in 0.9% saline.

4.7. Behavioral Tests:

4.7.1. Passive avoidance test (Manavi Chatterjee et al., 2012) :

1. The mice were subjected to a single trial passive avoidance test as described earlier. Briefly, each experimental mouse was placed in the lighted compartment of an automated shuttle box controlled by a software program PACS 30.
2. An automated guillotine door separated the light compartment from the dark compartment. After acclimatization period of 30 s in the lighted compartment, the guillotine door was automatically opened. As soon as the animal entered the dark compartment, thedoor was shut automatically and the subject received a low intensity foot shock (0.5 mA; 10 s).
3. Infrared sensors monitored the transfer of the animal from one compartment to another and were recorded as transfer latency time (TLT) in seconds. The 1st trial, was conducted for acquisition and the 2nd trial for retention testing. There was a 24 hr interval between the 1st trial and the 2nd trial. The learning ability of the animal was determined from an increase in the TLT during the 2nd trial (retention) as compared to the 1st trial (acquisition).

4.7.2. Forced Swimming Test (Seema singh et al.,2012)

1. Forced swimming test, as described previously in mice is a measure of despair behaviour.
2. In brief, mice were placed individually in glass cylinders (20 cm height, 10 cm diameter) containing 10 cm depth of water at 25°C.
3. After 5 minutes, the animals were removed from water, dried and returned back to their home cages. They were again placed in the cylinder 24 hr later and after the initial 1 min acclimatization period, the total duration of immobility was measured for 5 mins.
4. The duration of swimming during the 5-min test period was automatically recorded by a camera mounted above the cylinders and stored on a computer equipped with the relevant software

5. CONCLUSION

Schizophrenia is the most debilitating and mental illness and affects approximately 1% of the population in the world. Many patients with this life-altering and chronic illness either not respond well to current treatments, or experience side effects which make medication compliance an issue. This article gives brief explanation about the pathophysiology, treatment and various animal models for Schizophrenia. Numerous animal models are available in order to induce Schizophrenia but the question remains unclear that which animal model would be the most appropriate animal model suitable to the humans.

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