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Review Article

NON-BEHAVIORAL MODELS OF PSYCHOSIS

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ABSTRACT

Animal models have become indispensible tools for discovering new medicines and in the analysis of multitude of causes, bio-markers and pathophysiological changes, which bring about symptoms characteristics of a specific disorder. One of the biggest challenges in discovering medicines for psychosis is to find an appropriate animal model of this illness possessing fair face validity, construct validity, and predictive validity. We had explained in detail behavioral models of psychosis in our previous article. In the present review article, the authors have described various non-behavioral models such as pharmacological models (administering specific chemicals), genetic models (through genetic manipulation), lesion models (lesion of selected brain parts) and neuro-developmental models employed for screening anti-psychotic agents. All these animal models imitate schizophrenic defects in some manner. Traditionally, pharmacological models (drug/chemical-induced psychosis) were the most widely used. These models involve the manipulation of dopaminergic, glutamatergic, serotonergic, or GABA-ergic systems. In Lesion models, selected area of an animal's brain is damaged, to induce psychosis-like symptoms. Genetic factors also play a prominent role in many psychiatric disorders and numerous putative candidate genes have been identified. Neurodevelopmental models are based on the fact that schizophrenia can be caused due to prenatal exposure to certain viruses. The animals usually employed for the development of these models include rats, mice, and primates. The specific animal models developed within these frameworks are described in this review article.

Keywords: neurotransmitter, schizophrenia, lesion, amphetamine, psychosis.

INTRODUCTION

Mental disorders have become highly prevalent due to ambitious lifestyle, urbanization and stressful environment. Around 12% of the world's population is currently afflicted by one or the other mental disorder. Mental disorders include major depression, schizophrenia, bipolar disorder, obsessive compulsive disorder, Alzheimer's disease, anxiety, etc. These disorders can develop at any age and in individuals of any race, religion or income group. Psychiatric disorders create a maladaptive pattern of thoughts, feelings, and behaviors, which lead to strained relationships and disrupted professional life. The causes of psychiatric disorders can be attributed to heredity, stress, drug abuse or traumatic injury. Medications and counseling can help in alleviating these mental disorders. Animal models have become indispensible tools for discovering new medicines and in the analysis of multitude of causes, bio-markers and pathophysiological changes, which bring about symptoms characteristics of a specific disorder. One of the biggest challenges in discovering medicines for psychosis is to find an appropriate animal model of this illness possessing fair face validity, construct validity, and predictive validity. We had explained in detail the behavioral models of psychosis in our previous article. [1] In the present review article, the authors have described various non-behavioral models such as pharmacological models (administering specific chemicals), genetic models (through genetic manipulation), lesion models (lesion of selected brain parts) and neuro-developmental models. Emphasis is placed on the critical evaluation of these models because these models would help in shaping the direction of future research.

Pharmacological models (Drug / Chemical induced psychosis)

Pharmacological models of schizophrenia are derived from our current understanding of the alterations in various neurotransmitter systems.

Dopaminergic Agonist

The dopamine (DA) hypothesis of schizophrenia proposes that dysfunction in DA neurotransmission is the underlying cause of the symptoms of the disorder. Specifically, hyperactivity of mesolimbic dopaminergic neurons is suggested to produce the positive symptoms of schizophrenia. A hypo-dopaminergic state in the frontal-cortical terminal fields of mesocortical DA neurons has also been proposed to be the basis of negative symptoms[2].

Amphetamine group Toxicity[3]

Species: Male mice (NMRI, Ivanovas)

Figure 1: Male Mice

Indicative Behavior: Increased behavioral activation followed by death

End Point: Neuroleptics reduce the death rate.

Principle: Amphetamine is an indirectly acting sympathomimetic amine, which exerts its effects primarily by releasing norepinephrine from the storage sites in the sympathetic nerves. After administration of high doses of Amphetamine (20mg/kg s.c) mice exhibit an elevated motor behavior, which is highly increased by aggregation. This increase in behavioral activation is followed by death within 24h in 80-100% of animals. Neuroleptics (10mg/kg chlorpromazine and 1mg/kg haloperidol p.o.) reduce this death rate.

Procedure: Male mice are dosed with the test compound / anti-psychotic agent and are placed in glass jars of 18 cm diameter. Untreated animals serve as the control animals. The test has to be performed at room temperature of 24 °C. Thirty min after i.p. or 1 h after oral administration of the drugs, the mice receive 20 mg/kg d-amphetamine s.c. The mortality is assessed 1, 4 and 24 h after dosing.

Special Points: Non-neuroleptics, sympatholytics and sedatives like barbiturates do not produce a dose related protection in this model. Benzodiazepines are also found to be ineffective in the prevention of amphetamine group toxicity. Thus, it is a reliable method for detecting the activity of neuroleptics drugs.

Inhibition of Mouse Jumping[4]

Species: Male mice (NMRI, Ivanovas)

Indicative Behavior: Peculiar jumping response

End Point: Neuroleptics block jumping response

Principle: Jumping response was described in mice after administration of L-dopa in amphetamine pretreated animals, where the number of jumps can be objectively counted. The mouse jumping is due to dopaminergic overstimulation. The phenomenon can be blocked by neuroleptics.

Procedure: Male mice are injected with 4 mg/kg d-amphetamine sulfate, followed 15 min later by an i.p. injection of 400 mg/kg L-dopa. The mice spontaneously begin to jump at a high rate. A median of 175 jumps can be observed in these mice during 60 min period. Since, mice do not show any jumping behavior after saline administration, the responses after drug administration are specific. It can be measured automatically through a pressure-sensitive switch closure or properly positioned photoelectric beam disruptions. Test compounds are administered 60 min prior to L-dopa injection. Jumps of mice treated with test drugs or standard drugs are counted and expressed as percentage of jumps in amphetamine/ L-dopa treated animals.

Special Point: The method is sensitive and specific for neuroleptic drugs

Inhibition of Amphetamine Stereotype in rats[5]

Species: Wistar rats

Indicative Behavior: Stereotypic behavior (continuous sniffing, licking, chewing or compulsive gnawing)

End Point: Neuroleptics reduce or abolish stereotypic behavior

Principle: Amphetamine, an indirectly acting sympathomimetic agent induces stereotypic behavior in rats (10mg/kg s.c) which is characterized by continuous sniffing, licking, chewing or compulsive gnawing. This behavior can be prevented by administration of neuroleptic agents (such as chlorpromazine 1.75 mg/kg i.p and haloperidol 0.2 mg/kg i.p).

Procedure: Rats are injected simultaneously with d-amphetamine (10 mg/kg s.c.) and the test compound i.p. Rats are then placed individually in stainless-steel cages (40 cm × 20 cm × 18 cm). The control groups receive d-amphetamine and vehicle. The animals are observed for 60 min after drug administration. Stereotypic behavior is characterized by continuous sniffing, licking, chewing or compulsive gnawing An animal is considered to be protected, if the stereotypic behavior is reduced or abolished. The percent effectiveness of a drug is determined by the number of animals protected in each group.

Special Point: Amphetamine-induced stereotypy in rats can be regarded as a simple method to detect neuroleptic activity. However, this may reflect the effects in the corpus striatum, which are thought to be responsible for the Parkinsonism-like side effects of neuroleptics.

Modification: A low dose of 2 mg/kg d-amphetamine i.p. induces both increased locomotion (thought to reflect an increased dopaminergic transmission in the nucleus accumbens) and weak stereotypy (thought to reflect an increased dopaminergic transmission in the neostriatum). The behavior is measured in a combined open field apparatus with holes on the bottom to measure nose-pocking and registration of time spent in the corners.

Inhibition of Apomorphine Stereotypic behavior in rats[6]

Species: Wistar rats

Indicative Behavior: Stereotypic behavior (licking, sniffing and gnawing in a repetitive, compulsive manner)

End Point: Neuroleptics reduce or abolish stereotypic behavior

Principle: Apomorphine induces a stereotypic behavior in rats, characterized by licking, sniffing and gnawing in a repetitive & compulsive manner, which is an indication of striatal dopaminergic stimulation. Compounds which prevent apomorphine-induced stereotypic behavior antagonize dopamine receptors in the nigrostriatal system (0.2 mg/kg haloperidol s.c. and 5.0 mg/kg chlorpromazine s.c.). Clozapine is ineffective even at high doses.

Procedure: Rats are administered the test drug or the standard drug i.p. 60 min prior to apomorphine dosage. Apomorphine HCl is injected s.c. at a dose of 1.5 mg/kg. The animals are placed in individual plastic cages. After the 10 min of apomorphine administration, a 10 sec observation period is used to measure the presence of stereotypic activity such as sniffing, licking and chewing. An animal is considered protected if this behavior is reduced or abolished. The percent effectiveness of a drug is determined by the number of animals protected in each group.

Modifications: Apomorphine induced stereotypic behavior is observed in a variety of species including pigeons. The symptoms in pigeons are manifested as pecking against the wall of the cage or on the floor. Modification was done by registering the pecking by a microphone, amplification through a pulse preamplifier and registration with a polygraph.

Inhibition of Apomorphine climbing in mice[7]

Species: Male mice (NMRI, Ivanovas)

Indicative Behavior: Peculiar climbing behavior characterized initially by rearing and then full-climbing activity

End Point: Neuroleptics antagonize apomorphine-induced climbing behavior

Principle: Administration of apomorphine to mice results in a peculiar climbing behavior, which is characterized initially by rearing and then full-climbing activity, predominantly mediated by the mesolimbic dopamine system. The ability of a drug to antagonize apomorphine-induced climbing behavior in the mouse has been correlated with neuroleptic potential.

Procedure: Male mice are treated i.p. or orally with the test substance or the vehicle and placed individually in wire-mesh stick cages. 30 min afterwards, they are injected s.c. with 3 mg/kg apomorphine. Then, after 10, 20 and 30 min of apomorphine administration, they are observed for climbing behavior and scored as follows:

Behaviour	Score
0	Four paws on floor
1	Fore (two) feet holding the vertical bars
2	All Four feet holding the bars

The average values of the drug-treated animals are compared with those of the control animals and the decrease is expressed as percent.

Inhibition of Apomorphine Induced Emesis in dogs [8]
Species: Beagle dogs
Indicative Behavior: Emetic
End Point: Neuroleptics block emesis
Principle: Emesis is defined as wretching movements followed by an opening of the mouth and either attempted or successful ejection of stomach content. The blockade of centrally acting dopaminergic mechanism is considered to play a major role in suppression of psychotic reactions in schizophrenia. Apomorphine (regarded as a direct dopaminergic agonist) produces a pronounced emetic effect in dogs. The blockade of apomorphine emesis is used as an indication of dopaminergic blockade.
Procedure: The dogs are given the test compounds in a gelatin capsule. They are then dosed with 0.15 mg/kg apomorphine s.c, at various intervals after administration of the test compound. The dogs are first observed for overt behavioral effects, e.g., pupillary response to light, changes in salivation, sedation, tremors, etc. Then, after the administration of apomorphine, the dogs are observed for stereotypic sniffing, gnawing and the emetic response. If the experimental compound is anti-emetic in the primary screen, the dose is progressively lowered to obtain a minimal effective dose or an ED50 value. The ED50 values for haloperidol and chlorpromazine were found to be 0.06 mg/kg p.o. and 2.0 mg/kg p.o., respectively. Clozapine was not effective at doses between 2 and 10 mg/kg. p.o.
Special Point: Both anti-emetic and anti-psychotic activities are thought to be due to dopaminergic blockade. The sites of action and the areas of brain appear to be different and lack complete correlation to these activities.

Purposeless Chewing in rats[9, 10]
Species: Wistar rats
Indicative Behavior: Purposeless chewing
End Point: Neuroleptics induce chewing behavior
Principle: Purposeless chewing can be induced in rats by cholinergic drugs or cholinesterase inhibitors, which can be blocked by anti-muscarinic agents. The chewing behavior has been proposed to be mediated through central M2 receptors rather than via central M1 site. Chewing can also be induced by chronic administration of neuroleptics in rats. Purposeless chewing is mediated by dopaminergic and nicotinic mechanisms.
Procedure: Rats are placed individually in a large glass cylinder (height 30 cm, diameter 20 cm) at 21 ±1°C and allowed to habituate for 15 min before injection of drugs. The antagonists like sulpiride or mecamylamine are given as standard drugs at different doses, 30 min before treatment either with 0.01 mg/kg nicotine or 1 mg/kg i.p of pilocarpine. Number of chewings are counted by direct observation immediately after drug administration. The results are presented as number of chewings in a 30 min period.
Modification: Tremulous jaw movements induced by tacrine can be antagonized by antipsychotic drugs.

Yawning/penile Erection Syndrome in rats[11, 12]
Species: Wistar rats
Indicative Behavior: Yawning/penile erection
End Point: Neuroleptics antagonize yawning/penile erection syndrome
Principle: Yawning is a fixed innate motor pattern characterized by a slow, wide opening of the mouth. A penile erection is considered to occur when the following behaviours are present: repeated pelvic thrusts followed by an upright position, an emerging, engorged penis, which the rats proceed to lick while eating the ejaculate. Yawning is a phylogenetically old, stereotyped event that occurs alone or associated with stretching and/or penile erection in humans and in animals (from reptiles to birds and mammals under different conditions). The yawning/penile erection syndrome can be induced in rats by apomorphine and other dopaminergic autoreceptor stimulants and can be antagonized by haloperidol and other dopamine antagonists. Antagonism against this syndrome can be regarded as indication of anti-psychotic activity. Besides the dopaminergic system, serotoninergic, cholinergic and GABA-ergic systems are also involved.
Procedure: Male rats are housed under controlled 12 h light-dark cycle with free access to standard food pellets and tap water. Rats are pretreated with subcutaneous injection of the antagonist 30 min prior to injections of the agonist, such as apomorphine (0.02 to 0.25 mg/kg s.c.) or physostigmine (0.02 to 0.3 mg/kg s.c. or i.p.). After administration of the agonist, rats are placed in individual transparent perspex cages. A mirror is placed at a suitable place to facilitate the observation of the animals for penile erections and yawns. The number of penile erections and yawns are counted for 30 min following the last injection. The results are expressed as the mean number of yawns or penile erections per group. The statistical significance is determined by comparing the results of each group with the results of the relevant control group.

Glutamatergic antagonists
Phencyclidine (PCP) and other N-Methyl-D-aspartate (NMDA) receptor antagonists induce schizophrenia like symptoms in healthy subjects and precipitate psychoses in patients with schizophrenia who have stabilized. This has led to the suggestion that schizophrenia may involve hypofunction of NMDA receptors.

Antagonism of MK-801 induced locomotion and falling in mice[13]
Species: Male mice (CD-1)
Indicative Behavior: Characteristic stereotypy in mice marked by locomotion and falling behavior.
End Point: Neuroleptics antagonize MK-801-induced stereotypy.
Principle: MK-801, a non-competitive NMDA antagonist, induces a characteristic stereotypic in mice marked by locomotion and falling mediated both dopamine dependent and dopamine independent mechanisms. Anti-psychotic agents antagonize this MK-801 induced stereotypic behavior.
Procedure: Male mice are individually placed in activity boxes lined with wire mesh flooring and allowed to acclimatize for 60 min. The animals are then dosed with the compounds 30 min prior to subcutaneous administration of MK-801 at 0.2 mg/kg. The mice are observed for locomotion and falling behavior for 15 min, following MK-801 administration.

Phencyclidine-induced Social Withdrawal Measured in the Social interaction Test[14]

Species: Wistar rats

Indicative Behavior: Stereotypic behavior, hyperactivity and social withdrawal

End Point: Neuroleptics antagonize stereotypic behavior (such as sniffing, grooming of partner, genital investigation), hyperactivity and social withdrawal

Principle: Phencyclidine (PCP) is a psychomimetic compound that can induce schizophrenia-like psychosis in humans. PCP treatment induces stereotypic behavior, hyperactivity and social withdrawal in rats, which can be inhibited by antipsychotic drugs.

Procedure: Phencyclidine (PCP) treatment induces stereotypic behavior, which can be evaluated in the social interaction test. The test appears to be specific for antipsychotic drugs and can be distinguished for effects on positive and negative symptoms. In the PCP induced social withdrawal test, native rats are housed in pairs for 10 days prior to the start of the test. During the test, one cage mate (familiar rat) is removed and new one (intruder) is placed in cages for duration of 10 min. The amount of the social interaction and locomotor activity, both for the resident and intruder is recorded for 10 minutes. Social interaction is measured as the total time spent on various elements of the interaction, i.e. sniffing, grooming of partner, genital investigation and following the partner. Apart from the locomotor stimulant effects, PCP in a dose of 1-2 mg/kg, decreases the time of social interactions. The doses used in this test are slightly lower than the doses required for inducing locomotor stimulation.

Special Point: The test helps to show the efficacy of anti-psychotic drugs against negative symptoms of schizophrenia.

Ketamine Induced Stereotypic behaviour in mice[15]

Species: Albino mice

Indicative Behavior: Stereotypic behavior (turning, weaving, and head bobbing)

End Point: Neuroleptics antagonizes stereotypic behavior (such as turning, weaving, and head bobbing)

Principle: Ketamine is classified as an NMDA receptor antagonist. Glutamate-blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with thedisorder. Reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function. Glutamate can affect dopamine function, which has been implicated in schizophrenia.

Procedure: Mice are injected simultaneously with d-amphetamine (10 mg/kg s.c.) and the test compound i.p. and are then placed individually in stainless-steel cages (40 cm×20 cm×18 cm). The control groups receive Ketamine (50mg/kg, i.p) and vehicle for 14 consecutive days. The animals of standard group receive Ketamine (50mg/kg, i.p) for 14 consecutive days and standard drug after 30 min on 14th day. The animals of test group receive Ketamine (50mg/kg, i.p) for 14 consecutive days and standard drug along with the test drug (i.p. or oral route). The stereotypic behavior is assessed by counting the number of turning, weaving, and head bobbing. Turning is measured by counting turn around behavior of neck every 10 min for 60 min. Weaving and head bobbing are measured by counting its neck wave right and left, and go up and down every 10 min for 60 min. Ataxia is assessed by counting the number of fall over four feet (falling) every 10 min for 60 min. Locomotor activity (counts) of the mice is measured every 10 min for 60 min with an animal activity meter. Locomotor activity is also assessed by counting the number of line-crossings.

Prepulse Inhibition of Startle Response[16, 17]

Species: Male Sprague Dawley rats

End Point: Neuroleptics antagonize prepulse inhibition (PPI) disruption

Principle: Prepulse inhibition is a model of sensori-motor gating, which can be assessed in both animals and humans using the startle reflex response. When a fixed startle eliciting stimulus (i.e the pulse) is preceded by 30–500msec by a weak, non-startle-eliciting stimulus (i.e., the prepulse), the magnitude of the startle response is significantly reduced to the pulse alone. Schizophrenic patients have decreased prepulse inhibition relative to normal control subjects, and this is thought to reflect impairment in their ability to filter irrelevant sensory stimuli. Similar reductions in prepulse inhibition are produced in rats by administration of psychotomimetic drugs such as the dopamine agonists, amphetamine and apomorphine or the non-competitive NMDA antagonists phencyclidine and dizocilpine (MK801).

Procedure: Male rats are treated with various doses of test compound or saline (s.c). Immediately after that rats receive a second s.c. injection consisting of 2 mg/kg d- amphetamine, or 0.5 mg/kg apomorphine, or 0.1mg/kg dizocilpine or saline. Then, 10 min later, animals are placed in special startle chambers. Startle chambers consist of a Plexiglas cylinder 8.2 cm in diameter resting on a (12.5 × 25.5 cm) plexiglas frame within a ventilated enclosure housed in a sound-attenuated room exposed to 70-dB background noise. After a 5-min acclimation period, acoustic stimuli are presented via a speaker mounted 24 cm above the animal. Acoustic stimuli consisted of a 120-dB pulse by itself (pulse alone) or a 120-dB pulse preceded by 100 msec prepulses 3, 5, and 10 dB above background noise. There was an average of 15 s between stimuli. A piezoelectric accelerometer mounted below the Plexiglas frame detects and transduced the motion within the cylinder. Startle amplitude is defined as the degree of motion detected by this accelerometer. Each rat is tested on four separate occasions separated by 7 non-test days. On each test day, the dose of test compound is kept constant, but the specific psychotomimetic agent is alternated across test days in a counterbalanced fashion. Prepulse inhibition is calculated as the percentage of the pulse-alone startle amplitude using the following formula: [1 – (startle amplitude after prepulse–pulse pair/startle amplitude after pulse only)] × 100.

Special Point: Most anti-psychotics are able to antagonize prepulse inhibition disruption produced by dopamine agonists, whereas prepulse inhibition disruption by NMDA antagonists may be selectively sensitive to anti-psychotics with atypical features. Haloperidol failed to block the effects of phencyclidine and dizocilpine prepulse inhibition of startle.

Latent Inhibition[18, 19]

Species: Male Sprague Dawley rats

End Point: Neuroleptics suppress latent inhibition (retarded acquisition of a conditioned response that occurs if the subject being tested is first pre-exposed to the to-be-conditioned stimulus without the paired unconditioned stimulus)

Principle: Latent inhibition has been recommended as an animal model of schizophrenia. Latent inhibition refers to the

retarded acquisition of a conditioned response that occurs if the subject being tested is first pre-exposed to the to-be-conditioned stimulus without the paired unconditioned stimulus. Because the "irrelevance" of the to-be-conditioned stimulus is established during non-contingent pre-exposure, the slowed acquisition of the conditioned stimulus–unconditioned stimulus association is thought to reflect the process of overcoming this learned irrelevance. Latent inhibition has been reported to be diminished in acutely hospitalized schizophrenic patients. Several authors, which used the latent inhibition model in rats to test psychotropic compounds, tested the effects of selective D1 antagonists on latent inhibition in the rat.

Procedure: Male rats are housed in a cage under a12-h reversed cycle (dark & light) with food and water ad libitum. All experimental manipulations are carried out in the dark phase of the dark/light cycle. Modified metal Skinner boxes {(24.5 × 24.5 × 21cm) measured from a raised grid floor} are located in darkened, sound-insulated and ventilated outer boxes. A removable water bottle is located on one side of each Skinner box through a hole of 1.0cm diameter, positioned 2 cm above the grid floor. When water is not required, the water bottle is removed. Licks (the spout of each water bottle) are recorded using a lickometer (model 453, Campden Instruments, London,UK). The pre-exposed stimulus is a flashing light (10 s duration with three light flashes per second) situated in the middle of the roof of each Skinner box. The grid floor consisted of steel bars (0.5cm in diameter) spaced 1 cm apart. Shock generators with scramblers are calibrated to produce 0.5-mA shocks via the grid floor.

Modification: Rats are randomly assigned to experimental groups and are allocated to a particular Skinner box. They have experience of the box only for the duration of the experiment. After adaptation to the housing conditions for 1 week, rats are placed immediately on a 23-h water deprivation schedule that continued until the end of the experiments. Food remained freely available.

Baseline days (days 15–19)

After 7 days on the water deprivation period, 5 days of pre-training commenced. Each rat is placed in a Skinner box for 15min. The water bottle is present and each rat can drink freely. After the baseline session is over, each rat is returned to its home cage and allowed access to water for 45min.

Pre-exposure (day 20)

With the water bottle removed, each rat is placed in a Skinner box. Rats receive ten stimulus (flashing house-light) presentations of 10 s duration (three light flashes per second) with a fixed stimulus interval of 50 s. Afterwards the rats are returned to their home cages and allowed access to water for 1 h.

Conditioning (day 21)

With the water bottle removed, each rat is placed in a Skinner box. Then, 5 min later, each rat receives the first of two light foot-shock pairings. House-light parameters are identical to those of the pre-exposure period. The house-light is immediately followed by the foot shock (0.5mA for 1 s). The second light-shock pairing is given 5 min later. After the termination of the conditioning period, animals are returned to their home cages and allowed access to water for 1h.

Re-baseline day (day 22)

With the water bottle present, each rat is placed in a Skinner box and allowed to drink as in the baseline sessions.

Test day (day 23)

With the water bottle present, each rat is placed in a Skinner box and allowed to drink. When each rat completes 75 licks, the flashing house-light is presented and continued until 5min had elapsed from stimulus onset. Time bins of 30s duration commenced from the time of stimulus presentation and the number of licks made by each rat within every time bin is recorded. This measure allowed the pattern of drinking over the course of stimulus presentation to be shown. The amount of suppression of licking for each rat is assessed using a suppression ratio calculated from the time (in seconds) to complete licks 51–75 (pre-stimulus) divided by the time (in seconds) to complete licks 51–100 (pre-stimulus + stimulus on). A suppression ratio of 0.01 indicates total suppression of licking (no latent inhibition), while a ratio of 0.5 indicates no change in licking rate from the pre stimulus period to the stimulus-on period (latent inhibition).

Drug Treatment

Test drugs or vehicle are administered by subcutaneous injection in various doses 30 min prior to pre exposure and conditioning.

Times to complete licks and the suppression ratios are analyzed independently using a 2 × 6 ANOVA with main factors of pre-exposure and drugs.

Serotonin-Agonists[20]

The serotoninergic (5-HT) system has also been frequently implicated in schizophrenia. The 2 major classes of psychedelic hallucinogenic drugs, the indoleamines (e.g., lysergic acid diethylamide [LSD]) and phenethylamines (e.g., mescaline), are believed to mediate their effects through 5-HT_{2A} receptors. LSD has been shown to disrupt startle habituation and PPI in humans and rats. Further, this effect is believed to be mediated through direct stimulation of 5-HT_{2A} receptors. Indeed, the disruptive effects of PCP (Phencyclidine) on PPI (Prepulse inhibition) have also been proposed to be mediated through indirect activation of 5-HT_{2A} receptors. The relatively high affinity of atypical anti-psychotics such as clozapine for the 5-HT_{2A} receptor supports a role of 5-HT systems in schizophrenia.

GABA- Antagonists

The $GABA_A$ receptor antagonist picrotoxin has been shown to reduce PPI in rats when injected into the medial PFC. Further, pretreatment with the DA antagonist haloperidol antagonized this effect, suggesting that blockade of GABA receptors in PFC (prefrontal cortex) impairs sensorimotor gating in a DA-dependent manner. However, the lack of any other reported GABA-induced behavioural deficits related to schizophrenic symptoms makes the face and predictive validity of this model difficult to establish.

Lesion models

Prefrontal lesions

Patients suffering from schizophrenia display cognitive deficits, which are attributed to dysfunction of prefrontal cortical areas**.** Cortical lesions in non-human primates and in rats result in cognitive dysfunctions pertaining to planning, strategy and goal directed behaviors similar to those seen in schizophrenia. Neonatal cortical lesions in rats result in post-

pubertal increased locomotor activity to a novelty stressor or a dopaminergic agonist, and an enhanced DA release in the accumbens nucleus after stress.

Neonatal Ventral Hippocampal Lesion

Neonatal ventral hippocampal (nVH) lesions in rats result in adult onset of a number of behavioral and cognitive abnormalities analogous to those seen in schizophrenia such as deficits in working memory, sensori-motor gating and social interaction including hyper-responsiveness to stress and psychostimulants. Neonatal ventral hippocampus lesion alters the dopamine content in the limbic regions in postpubertal rats. However, despite the enhanced locomotor response to amphetamine in these rats, dopamine release is attenuated in both the prefrontal cortex and nucleus accumbens in response to amphetamine or stress in these animals. In a similar model involving neonatal temporal lobe lesions in primates, prefrontal cortex regulation of dopamine release in the nucleus accumbens is disrupted. Neonatal ventral hippocampus lesions have also been reported to be associated with increased sensitivity to D_2 receptor agonists such as quinpirole, and altered levels of dopamine receptors have been reported in various brain regions in this model.

In contrast, most of the research on neonatal lesion models of schizophrenia has focused on the ventral hippocampus. This is not surprising given the major role of this region in regulating subcortical dopamine level. Rats with neonatal excitotoxic lesions of the ventral hippocampus demonstrate delayed onset of hyperdopaminergic behaviours. Although, these animals are behaviorally similar to controls at postnatal day 35 and at postnatal day 56, they display increased locomotion in response to novelty, forced swim stress and after saline or amphetamine injection. Interestingly, these behavioural effects are not observed after neonatal DH lesions. The postpubertal changes induced by neonatal ventral hippocampus lesions are believed to be the result of increased mesolimbic dopaminergic function and reduced dopamine release. The Postnatal day 56 rats also exhibit reduced haloperidol-induced catalepsy and enhanced apomorphine-induced stereotypy. As in the case of dopaminergic pharmacological models, rats with ventral hippocampus neonatal lesions also show impaired PPI. Further, the behavioural deficits exhibited by these animals are ameliorated after antipsychotic administration.

Lesions in limbic structures

Imaging studies in schizophrenic patients have shown volume reductions in several limbic structures (e.g. hippocampus, amygdala). Together with the evidence from functional and pharmacological studies, lesioning limbic structures (i.e. nucleus accumbens, amygdala, hippocampus, and nucleus basalis magnocellularis) have been an approach that has received much attention. In rats these lesions result in a grossly similar syndrome, mimicking several aspects of schizophrenia. These include (but are not limited to) disturbed PPI, changed mesolimbic dopamine function, enhanced sensitivity to dopaminergic agonists, disturbed social behavior, and disturbed behavioral performance in place navigation and spatial tasks.

Models of genetic etiology[21, 22]

Genetic factors play a prominent role in many psychiatric disorders and numerous putative candidate genes have been identified. Neuregulin-1 (NRG-1) is a leading candidate gene for schizophrenia that is involved in various aspects of brain development and function. It is unclear, however, how the implicated risk variants effect the expression and function of the gene. A heterozygous Nrg-1 knockout mouse, lacking the transmembrane domain of the gene, shows locomotor hyperactivity, impaired PPI and decreased expression of NMDA receptors. Yet other studies indicate that increased NRG-1 signaling can lead to abnormalities related to schizophrenia, such as reduced activation of NMDA receptors. Other factors that complicate the interpretations of genetic mouse models or environmental variables are genetic background onto which the mutation is introduced, and flanking genes introduced via the embryonic stem cell donor. The recent findings suggest that one of the most widely used mouse strains carry a mutation in Disc1, the orthologue of a leading schizophrenia candidate gene. Despite the fact that these models are based on rare genetic events, they may be helpful in identifying cellular pathways and neural circuits dysfunctional in schizophrenia in general and they will be integral in constructing a framework to analyze other models that are likely to appear in near future.

Neurodevelopmental models (Prenatal defects related models) [23]

Brain development is a continuous process. Postmortem brain studies across the lifespan document the striking time and region of specific genes expressed in schizophrenia. Clinical, epidemiological and translational studies continue to link prenatal infection and schizophrenia. Prenatal exposure to rubella, toxoplasma and herpes simplex virus type 2 are established causes of developmental disorders, including mental retardation, learning disabilities and sensori-neural dysfunction including psychosis. Neurodevelopmental animal models include maternal immune activation and prenatal malnutrition. GABA A receptors have been reported to be missing from the hippocampus of adult offspring subjected to maternal malnutrition, interruption of neurogenesis by methylazoxymethanol and the neonatal ibotenic acid lesion of the ventral hippocampus. Additional models can be developed by the exposure of pregnant mice to unpredictable stress, maternal separation or birth complications. All of these models have revealed behavioral deficits associated either with positive, cognitive or negative symptoms of schizophrenia, and alterations in the dopaminergic, glutamatergic, GABAergic and serotonergic systems. A large number of studies find some relationship between obstetric complications and later onset of schizophrenia. Obstetrical events may be causal in themselves or reflect other causal processes.

CONCLUSION

Schizophrenia continues to be a mysterious disease, fascinating the minds of psychiatrists, pharmacologists and neuroscientists all over the world for more than a century. The risk of developing schizophrenia is almost equal in men and women, but gender differences do exist in the initial age of onset of the disease. Schizophrenia is characterized by three general types of symptoms: Positive symptoms (psychosis), Negative symptoms and Cognitive symptoms. Not all schizophrenic patients exhibit each of these symptoms, nor are these symptoms exclusive to schizophrenia. Animal models in the area of psychopharmacology are difficult to develop because of complexity of the human brain. Therefore, it is an ardent task to produce schizophrenia or psychosis in laboratory animals, since their brain is not so well developed. At present, there is

no perfect animal model available for screening of anti-psychotic agents. Therefore, it has become very difficult to discover new medicines useful in the treatment of psychosis. An ideal animal model of psychosis should have reasonable analogy to the human disorder in its manifestations. This laboratory model should be able to elicit behavioral changes in animals that can be quantified; and these behavioral changes observed in animals should be reversible by the same treatment modalities that are effective in humans. We had explained in detail the behavioral models of psychosis in our previous article. In the present review article, the authors have described the ways and methods of producing psychotic symptoms in laboratory animals under the subheadings pharmacological models (administering specific chemicals), genetic models (through genetic manipulation), lesion models (lesion of selected brain parts) and neuro-developmental models. All these animal models imitate schizophrenic defects in some manner.

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