



BEHAVIORAL MODELS OF PSYCHOSIS

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ABSTRACT

Existing research into schizophrenia has remained highly fragmented, much like the clinical presentation of the disease itself. Differing theories as to the cause and progression of schizophrenia, as well as the heterogeneity of clinical symptoms, have made it difficult to develop a coherent framework suitable for animal modeling. However, a few animal models have been developed to explore various causative theories and to test specific mechanistic hypotheses. Historically, these models have been based on the manipulation of neurotransmitter systems believed to be involved in schizophrenia. In recent years, the emphasis has shifted to targeting relevant brain regions in an attempt to explore potential etiologic hypotheses. In the present review article, we have described in detail various behavioral models available in literature for screening of antipsychotic agents. In the next article, we propose to focus on chemical induced psychosis (Pharmacological models). We have highlighted the principle, end point, brief procedures, merits and demerit of all the behavioral models in the foregoing pages. Emphasis is placed on the critical evaluation of currently available models because these models help to shape the direction of future research.

Keywords: Schizophrenia, Neuroleptic, Hibernation, Catalepsy

INTRODUCTION

Schizophrenia is a severely debilitating psychiatric disorder characterized by a combination of symptoms, often divided into positive (e.g., hallucinations, delusions, thought disorganizations), negative (e.g., loss of motivation, affective blunting, alogia, social withdrawal) and cognitive (e.g., deficits in attention, memory and executive functions) symptoms¹. Many patients with schizophrenia also experience a wide range of catatonic phenomena such as catalepsy, stereotypies, echopraxia, unusual posturing and mannerisms. About 1 % of the population suffers from schizophrenia worldwide and the risk increases for those, whose close family members have suffered with the disorder². Animal models provide the opportunity to decipher the relationships between the nervous system and animal behavior as they serve as obligatory tools for screening of drug tests³. The main advantage of animal models is to generate new pertinent hypotheses relevant to the human disorder opening the path for innovative research. Development of animal models is a crucial issue in biological psychiatry. One of the main hurdles for the development of animal models is to define a marker of the psychiatric disorder. Several markers have been suggested for schizophrenia, but for the moment no single marker or etiopathogenic mechanism can be solely attributed for it. The authors have studied in depth various animal models available in literature for schizophrenia. None of the current animal models of schizophrenia serve as the complete animal equivalent of the human disorder. Rather, they are often designed to test specific, causative or mechanistic hypotheses regarding schizophrenia. The models can be validated on the basis of how well their applications predict the performance of humans suffering from schizophrenia and whether the animal model provides a sound theoretical rationale. How accurately an animal model reproduces the symptoms of a human condition, is known as face validity. However, as will be discussed later, a variety of behavioral correlates in animals may serve as approximate indicators for psychiatric

disturbances in humans and could be useful to develop animal models relevant to schizophrenia.

Behavioral Models

Golden Hamster Test

Species: Male golden hamsters (*Mesocricetus auratus*)^{4,5}



Figure 1: Golden Hamster

Normal Behavior: Innate / Natural

Indicative Behavior: Aggressive behavior

End Point: Neuroleptics suppress the aggressive behavior / defense reactions (turning, vocalizing and biting)

Drugs: Chlorpromazine (1.5 mg/kg s.c.), Reserpine (0.2 mg/kg s.c.)

Brief Procedure

The animals are crowded together in Makrolon (R) cages for at least 2 weeks. During this time, the animals develop a characteristic aggressive / fighting behavior. For the test, animals are placed individually into glass jars of 2 liters. The hamsters assume a squatting and resting position during the day. If the animals are touched with a stick or forceps, they wake up from their day-time sleep and arouse immediately from the resting position. If one tries to hold the hamster with blunted forceps, the hamster throws himself onto his back, tries to bite and push the forceps away with his legs and utters angry shrieks (aggressive / fighting behavior). Touching the animals is repeated up to 6 times followed by punching with the forceps. Such animals responding to the

stimulus with all three defense reactions (turning, vocalizing and biting) are included into the test. The test compounds are applied subcutaneously, intraperitoneally or orally. The stimuli are applied every 20 minutes for 3 h. The suppression of the defense reactions is evaluated. Neuroleptics such as Chlorpromazine suppress the aggressive behavior/defense reactions.

Special Points

After each stimulation; the “tamed” animal is placed on an inclined board with 20 degree inclination. Normal hamsters and hamsters tamed by neuroleptics are able to support themselves or to climb on the board. Impaired motor function causes sliding down.

Merits

- Neuroleptics can easily be differentiated from sedatives and hypnotics.
- Anxiolytics with pronounced muscle relaxant activity also show no significant differences between taming and impaired motor function.
- Training of the animals is not required
- No expensive apparatus is needed.

Demerits

- Species specific (innate behavior of male golden hamsters)
- After each stimulation; the “tamed” animal is checked for impaired motor function.

Influence on Behavior of the Cotton Rat

Species: Cotton rat (*Sigmodon hispidus*)^{6,7}



Figure 2: Cotton Rat

Normal Behavior: Concealing / hiding in a tunnel

Indicative Behavior: Innate flight reflex / hiding behavior

End Point: Neuroleptics suppress the flight reflex / hiding behavior

Drugs: Chlorpromazine (1.5 mg/kg s.c.), Reserpine (0.2 mg/kg s.c.)

Brief Procedure

For the test, normal cages (25 cm x 30 cm x 20 cm) with a wire lid are used. A tunnel of metal sheet (half of a cylinder) 20 cm long and 7 cm high is placed into the cage. The cotton rats hide immediately in this tunnel. If the tunnel is lifted and placed on another site of the cage, the cotton rats immediately hide again. Three rats are placed in one cage and tested for their behavior. Selective shaving of the fur enables the observer to recognize each animal. If the rats behave as described, they are then treated with the test compound subcutaneously or orally. 15 minutes after application of the drug, the test period of 3 h is started. The tunnel is lifted and placed to another site. If the animals do not show the immediate flight reflex, an airstream of short duration is blown through the wire lid. If the animal still does not

respond with the flight reflex, it is considered to be positively influenced. Neuroleptics such as Chlorpromazine suppress the flight reflex / hiding behavior of cotton rats.

Special Points

The animal is placed on an inclined board with 35 degree of inclination and tested for disturbance of motor coordination. A normal animal is able to climb upwards. If coordination is disturbed the rat slides down.

Merits

- Method allows differentiation between neuroleptics, hypnotics and anti-anxiety agents
- Training of the animals is not required
- Simple and cost effective procedure.

Demerits

- Species specific (cotton rats)

Artificial Hibernation in Rats

Species: Male Wistar rats^{8,9}



Figure 3: Male Wistar Rat

Normal Behavior: Freely approach food and water

Indicative Behavior: Hibernating behavior

End Point: Artificial hibernation augmented by neuroleptics

Drugs: Chlorpromazine (1.5 mg/kg s.c.)

Brief Procedure

The rats are placed in ice-cold water to which surfactant is added in order to remove the air from the fur for 2 minutes. Then, the animals are placed into hermetically closed glass vessels of 750 ml volume, which are placed into a refrigerator at 2°C temperature. During each hour, the vessels are opened every 10 minutes for exactly 10 sec, allowing some exchange of air and reducing the carbon dioxide accumulation. At each time, animals are removed from the glass vessel and observed for signs of artificial hibernation (a state of reduced metabolism, muscle relaxation and a twilight sleep resembling narcosis, produced by controlled inhibition of the sympathetic nervous system and causing attenuation of the homeostatic reactions of the organism), which are not shown by control animals. Neuroleptics such as chlorpromazine enhance artificial hibernation behavior. Animal is considered to be showing the signs of artificial hibernation, when it remains on the back, even if the extremities are stretched out. In this state, cardiac and respiration frequency are reduced and the rectal temperature has fallen to 12–15°C. The rigor of the musculature allows only slow movements of the extremities. The animals recover completely within a few hours if they are brought to their home cages at room temperature. This kind of artificial hibernation was augmented by chlorpromazine.

Special Points

Under the influence of cooling and of hypoxic hypercapnia, the rectal temperature falls to 15°C and the animal is

completely anesthetized and immobilized. The rat can survive in this poikilothermic state for more than twenty hours.

Merits

- Training of the animals is not required
- Cost effective procedure.
- No special skills are required.

Demerits

- Result can be influenced by agents, which impair motor function.

Catatonias in Rodents

Species: Male Wistar or Male Sprague-Dawley rats, Nonhuman primates (Cebus monkeys)^{10,11}



Figure 4: Catatonia in Rat

Normal Behavior: Freely movable

Indicative Behavior: Unusual / Catatonic posture

End Point: Neuroleptics induce catatonia / unusual posture

Drugs: Haloperidol (1 mg/kg i.p.), Metoclopramide (20 mg/kg i.p.)

Brief Procedure

Catatonia in rats is defined as failure to correct an unusual (externally imposed) posture for a prolonged period of time. Neuroleptics, which have an inhibitory action on the nigrostriatal dopamine system, induce catatonia. While neuroleptics with little or no nigrostriatal blockade produce relatively little or no catatonic behavior. Animals are dosed intraperitoneally with the test drug or the standard. They are placed individually into translucent plastic boxes with a wooden dowel mounted horizontally 10 cm from the floor and 4 cm from one end of the box. The floor of the box is covered with approximately 2 cm of bedding material. The animals are allowed to adapt to the box for 2 minutes. After that each animal is grasped gently around the shoulders and under the forepaws. Then it is placed carefully on the dowel. The amount of time spent with at least one forepaw on the bar is determined. This time is recorded as the duration of catatonia. When the animal removes its paws, the time is recorded and the rat is repositioned on the bar. Three trials are conducted for each animal at 30, 60, 120 and 360 minutes. An animal is considered to be catatonic, if it remains on the bar for 60 s or more. Neuroleptics such as haloperidol and metoclopramide induce catatonia / unusual posture. For dose-response curves, the test is repeated with various doses and more animals.

Alternate Procedure

Two wooden blocks, one being 3 cm high and other 9 cm high are used in this test. Prephenazine is injected i.p to male

albino Sprague-Dawley rats. The severity of catatonic effect is observed as follows¹²:

Stage	Behavior	Score
I	Rat moves normally, when placed on table	0
II	Rat moves only, when touched or pushed	1
III	Rat placed on the table with one of the front paws raised on a 3 cm block, fails to correct the posture in 10 sec	0.5 for one paw with a total of 1 for this stage
IV	Rat placed on the table with one of the front paws raised on a 9 cm block fails to correct the posture	1 for each paw with a total of 2 for this stage

Observe the catatonia at 5, 15, 30, 45, 60, 90 and 120 minutes after prephenazine. For a single rat maximum possible score would be 4 revealing total catatonia. Neuroleptics such as prephenazine acting through blockade of dopaminergic receptors increase the catatonic score.

Special Points

Catatonic symptoms in rodents have been compared to the Parkinson-like extra pyramidal side effects seen clinically after administration of antipsychotic drugs.

Merits

- Phenomenon of catatonia can be used for measuring the efficacy and the potential side effects of neuroleptics
- No training of the animals is required
- Cheap and simple technique.

Demerits:

- For excellent results, the observer may be blind to the treatment given to the mice.
- This test seems to be particularly insensitive to the atypical neuroleptics like thioridazine and, especially, clozapine.

Modification

Catatonia induced by neuroleptic drugs can also be measured by the PAW test¹³, which measures increase in forelimb and hind limb retraction time in rats. This test is performed 30 minutes after intraperitoneal injection of test drug. Male Wistar rats are placed on a Perspex platform (30 × 30 cm with a height of 20 cm) containing two holes for the forelimbs (40 mm) and two for the hind limbs (50 mm) and a slit for the tail. The distance between the right and left forelimb holes is 15 mm and the distance between forelimb and hind limb holes is 55 mm. The rat is gently placed by placing the fore limbs and hind limbs in respective holes. The forelimb retraction time and the hind limb retraction time are defined as the time; the animal takes to withdraw one forelimb or one hind limb. The average forelimb retraction time and hind limb retraction time (the mean of three measurements) is calculated for each rat. The increase in hind limb retraction time was associated with the antipsychotic potential whereas, the increase in forelimb retraction time was associated with the potential to induce extra pyramidal side effects.

Pole Climb Avoidance in Rats

Species: Male rats of Wistar and Long-Evans strain^{14,15}

End Point: Neuroleptics enhance the time taken to climb the pole

Drugs: Chlorpromazine (3.0 mg/kg s.c.) Conditioned avoidance response (CAR)



Figure 5: Pole Climb Apparatus

Brief Procedure

The pole-climb apparatus is one of the most important laboratory models employed for the study of antipsychotic drugs. The pole-climb apparatus comprises of a chamber (25 cm × 25 cm × 40 cm) that is enclosed in a dimly lit, sound-proof box. This chamber has a grid floor (shock zone) to provide for mild electric shock to the rat and a wooden pole (2.5 cm in diameter) at the centre of the chamber, which forms shock free zone. A 2.8-kHz speaker and a 28-V light are situated on top of the chamber to provide for the bell sound or light. In a typical experiment, a rat is placed in the pole-climb apparatus and subjected to a neutral conditioned stimulus (CS) such as light or sound (usually a bell or a buzzer), followed immediately (after 20 sec) by an aversive unconditioned stimulus (US), such as a foot-shock (1.5 mA). During training sessions, a bell sound is always presented to the rat before delivering the scrambled electric shocks through the grid floor. Test sessions consist of 25 trials or 60 minutes, whichever comes earlier. The rat, after training sessions, soon learns to actively avoid the foot shock altogether by climbing on to the pole (shock-free zone) immediately after hearing the sound of the bell (shock avoidance response) even before the actual delivery of the electric shock. Thus, this rat is now fully trained to show conditioned avoidance response (CAR). These rats, when treated with low (non-cataleptic) doses of anti-psychotic drugs fail to climb on the pole after hearing the bell sound (CS), but do climb on the pole (escape response), when the foot shock is delivered through the grid floor. This selective disruption of avoidance behavior is characteristic of all anti-psychotic drugs, but neither anxiolytics nor antidepressants show this particular effect. On the other hand, the sedatives, like barbiturates totally block both, the anticipated shock avoidance response (Climbing on the pole after the bell) and the escape response (Climbing on the pole after delivery of foot shock). The rats pre-treated with barbiturates continue facing the bell sound and the foot shock and do not jump on to the pole at all. Furthermore, the ability of an anti-psychotic medicine to suppress the CAR has been shown to be closely correlated with its clinical potency. Thus, this apparatus can be used to distinguish anti-psychotic drugs (neuroleptics) from sedatives and anxiolytics. Whereas sedative compounds suppress both avoidance and escape behavior of animals at approximately the same doses, neuroleptic drugs reduce avoidance behavior at lower doses than those affecting escape behaviors.

Merits

- Highly specific for anti-psychotic medicines
- Used to separate neuroleptics from sedatives and anxiolytics.

Demerits

- Training of animals is required.
- Animals are subjected to electric shock, which is a painful procedure.

Foot-shock Induced Aggression

Species: Male mice (NMRI, Ivanovas)¹⁶

Indicative Behavior: Fighting behavior consists of vocalization, leaping, running, rearing and facing each other with some attempt to attack by hitting, biting or boxing.

End Point: Neuroleptics inhibit the aggressive behavior.

Drugs: Haloperidol (1.0 mg/kg i.p.)

Brief Procedure

This test employs mice, which fight after receiving foot-shock. Two mice are placed in a box with a grid floor consisting of steel rods at a distance of 6 mm. A constant current of 0.6 or 0.8 mA is supplied to the grid floor by a constant current shocker with an associated scrambler. A 60-Hz current is delivered for 5 sec followed by 5 sec intermission for 3 minutes. Each pair of mice is dosed and tested without previous exposure. The total numbers of fights are recorded for each pair during the 3 minutes period. The fighting behavior consists of vocalization, leaping, running, rearing and facing each other with some attempt to attack by hitting, biting or boxing. The test substance or the standard drug is applied either parenterally 30 minutes before the test or orally 60 minutes before the test. The percentage inhibition of aggressive behavior is calculated with respect to the control group. Neuroleptics such as haloperidol inhibit the aggressive behavior. This test is not specific for antipsychotics, since it shows positive results with anxiolytics as well as other psychoactive agents in addition to neuroleptics.

Merits

- Training of the animals is not required
- No sophisticated instrument is needed.
- Simple technique and require no special skills

Demerits

- This model also shows positive results with anxiolytics and other psycho-active drugs.
- Animals are subjected to electric shock.

Brain Self Stimulation

Species: Male Wistar rats^{17,18}

End Point: Neuroleptics suppress self stimulation of brain

Brief Procedure

Electrical stimulation of selected brain areas (such as posterior lateral hypothalamus) evoke effects, which are positively reinforcing and pleasure-some. Animals are anesthetized with pentobarbital (50 mg/kg i.p.) for permanent implantation of electrodes into the selected brain area of the rat with the help of a stereotactic instrument, dental drill and

dental cement. After allowing a minimum of 10 days for recovery, the animals are trained to press a lever for electrical stimulation of the brain on a continuous reinforcement schedule. The animals are ready for testing with standard agents after recording consistent baseline responses for 5 consecutive (30 minutes) sessions. The test drugs are administered 60 minutes prior to testing. Neuroleptics have been shown to be powerful blockers of self brain stimulation. Conversely, compounds that facilitate catecholaminergic transmission such as d-amphetamine and methylphenidate enhance self brain stimulation. Drugs that deplete brain catecholamines such as reserpine show inhibition (cessation) of self stimulation behavior.

Merits

- Neuroleptics have been shown to be powerful blockers of self stimulation. Conversely, compounds that facilitate catecholaminergic transmission such as d-amphetamine and methylphenidate enhance self brain stimulation.

Demerits

Complex procedure

CONCLUSION

Animal models help us to clarify complex mechanisms and provide a reasonably reliable platform to test the potential of new substances. They offer an opportunity to open a discussion between clinicians and biologists and shed new light through creative ideas that allow us to go beyond our usual way of thinking. We have discussed at length various animal models of psychosis in the present review article highlighting their merits, demerits, brief procedures, end-point etc in a lucid manner. In the next article, we propose to focus on chemical induced psychosis (Pharmacological models). Emphasis is placed on the critical evaluation of currently available models because these models help to shape the direction of future research. Current animal models of psychosis / schizophrenia are not intended to serve as the complete animal equivalent of the human disorder. Rather, they are often designed to test specific causative or mechanistic hypotheses regarding schizophrenia. Studies of these animal models can thus help us to construct models that are specific to the psychopathology and neurobiology of human behavior, opening the path to innovative hypotheses and research.

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