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ANIMAL MODEL IN PRECLINICAL RERSEARCH FOR ANTIPSYCHOTIC

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ABSTRACT

Preclinical animal models have a fundamental role in the discovery and development of antipsychotic drugs. These models enable researchers to assess efficacy, safety, pharmacodynamics and mechanisms of action before the human clinical trials begin. Schizophrenia and other psychotic disorders are complex neuropsychiatric phenomena and involve multiple disturbance of dopaminergic, serotonergic, glutamatergic, neurodevelopmental and inflammatory pathways. Due to the ethical and practical constraints for conducting experimental studies in humans, animal models are a necessary tool in translational psychiatry research. Various pharmacological, genetic, neurodevelopmental and behavioural models have been created to simulate various aspects of schizophrenia. Common models are amphetamine-induced hyperactivity, apomorphine-induced climbing behavior, phencyclidine (PCP)-induced psychosis, conditioned avoidance response (CAR) and prepulse inhibition (PPI) deficits. These models help distinguish between normal and abnormal antipsychotics as well as extrapyramidal side effects. Although currently, none of the models have an exact reproducibility of human schizophrenia, the combination of validated models enhances predictive accuracy and correlation with human conditions. Ethical compliance and adherence to regulatory guidelines further helps to increase scientific reliability. Continuous improvement of these models is important to the development of safer and more effective antipsychotic therapies.

INTRODUCTION

An animal model is a non-human species which is used for biomedical research for mimicking aspects of human diseases. Rodents like rats and mice are used most often because of some similar neurochemical pathways, ease of handling, short life cycle and characterized behavioral paradigms.

Animal models are of the following types

- Homologous models - emulating cause, symptoms, and response from treatment
- Isomorphic models - mimic symptoms, but not cause
- Predictive models - predict response to drug
- Spontaneous models - disease takes place naturally

These models allow you to perform experiments which would be ethically or practically impossible in people.

PRECLINICAL STUDIES

Preclinical development occurs before the clinical trials and is aimed at:

- Identify doses for subjects to begin with
- Evaluate the pharmacological activity
- Assess toxicity
- Mechanism of action Understanding

Regulatory authorities need preclinical data on safety and efficacy before data about drug efficacy or safety can be provided to humans.

SCHIZOPRENIA AND PSYCHOSIS OVERVIEW

Schizophrenia is a chronic and severe psychiatric disorder in which there are disturbances in thought, perception, emotion, and behavior. Psychosis is a major feature of schizophrenia and it is loss of contact with reality, including hallucinations, delusions, and disorganized thinking. The disorder often manifests itself during late adolescence or early adulthood and has a significant impact on social and occupational functioning. Schizophrenia symptoms are divided into three categories: positive symptoms (hallucinations and delusions), negative symptoms (withdrawal from social life, loss of motivation and reduced expression of emotion), and cognitive symptoms (impairment of memory, attention and executive functioning).

NEUROBIOLOGICAL MECHANISM

i. Dopamine Hypothesis

The dopamine hypothesis, strongly supported by the work of Arvid Carlsson, proposes that hyperactivity of dopamine transmission in the mesolimbic pathway contributes to positive symptoms of schizophrenia. The clinical efficacy of D_2 receptor antagonists supports this theory.

ii. Glutamate Hypothesis

Hypofunction of NMDA receptors contributes to cognitive and negative symptoms. NMDA receptor antagonists such as Phencyclidine induce schizophrenia-like behaviors in animals.

iii. Neurodevelopmental and Oxidative Stress Theories

Prenatal infections, early-life stress, and neurodevelopmental disturbances increase vulnerability to schizophrenia. Oxidative stress markers such as malondialdehyde (MDA) are elevated in experimental models.

CLASSIFICATION OF ANTI-PSYCHOTIC DRUGS

There are different types of Antipsychotics they are

1. Typical (First-Generation)

- Chlorpromazine
- Fluphenazine
- Haloperidol

These block mainly D2 receptors of dopamine and are linked with extrapyramidal side effects (EPS).

2. Atypical (Second-Generation)

- Clozapine
- Risperidone
- Quetiapine
- Olanzapine

They antagonize both D2 and 5-HT2A receptors, as well as having low EPS liability.

NEED OF ANIMAL MODELS IN THE STUDY OF ANTIPSYCHOTICS

Animal models are essential for

- Understanding neurotransmitters interactions.

- Screening novel compounds.
- Evaluating dose responses.
- Predicting the liability of side effects.
- Meeting the regulatory requirements before human tests.

CLASSIFICATION OF ANIMAL MODELS USED IN ANTIPSYCHOTIC RESEARCH

5.1 Pharmacological Models

These include administration of psychotomimetic agents

- Amphetamine-induced hyperactivity
- Apomorphine elicited climbing behavior
- PCP-induced psychosis model

These models mostly mimic positive symptoms.

5.2 Genetic Models

Genetic manipulation techniques are used such as gene knockout and transgenic mutation.

Major models include

- DISC1 mutant mice
- Neuregulin-1 (NRG1) mutants
- Mice genotypes (Dopamine transporter (DAT) knockout)
- NMDA receptor NR1 hypo mice

These models contribute to the understanding of the gene environment interactions.

5.3 Neurodevelopmental Models

These are **based on early disturbances of brain development.**

i. MAM Model

Prenatal treatment of methylazoxymethanol acetate interferes with cortical and hippocampal development.

ii. Model on Maternal Immune Activation (MIA)

Poly I:C administration mimic viral infection during gestation."

iii. Model of Neonatal Ventral Hippocampal Lesion (NVHL)

Early lesions in the hippocampus cause adult-onset behavioral abnormalities.

5.4 Behavioral Models

- Conditioned avoidance response(car)
- Prepulse Inhibition (PPI)
- Social interaction test
- Novel object recognition

BEHAVIORAL EVALUATION PARAMETER

i. **Locomotor Activity**

Hyperlocomotion induced by amphetamine is decreased by effective antipsychotics.

ii. **Conditioned Avoidance Response- CAR**

Selective suppression of the avoidance without inhibition of escape response is a good predictor of clinical efficacy.

iii. **Catalepsy Test**

- Measures EPS liability.
- Haloperidol has good catalepsy effects, Clozapine has little effect.

iv. **Prepulse Inhibition (PPI)**

Measurement of intellectual skills Testing the following reflexes: Evaluates sensorimotor gating deficits Impaired gating is restored by antidepressants.

v. **Social Interaction Test**

Assesses Negative-like symptoms, i.e. social withdrawal

PHARMACOLOGICAL AND NEUROCHEMICAL PARAMETERS

1. **Receptor Binding Studies**

- D2 receptor affinity (Ki value)
- 5-HT2A/D2 affinity ratio
- ED50 determination
- Computation of the therapeutic index

2. **Neurochemical Assessment**

- Concentrations of Dopamine (striatum, prefrontal cortex)
- Glutamate and GABA balance
- Oxidative stress: (MDA, SOD, GSH)

MOLECULAR AND HISTOPATHOLOGICAL EVALUATION

Molecular and histopathological studies give a deeper insight on the mechanism-of-action of the antipsychotic drugs in preclinical research. While testing reveals improvement in behavior, molecular analysis establishes the fact of changes at the cellular and genetic level. Gene expression studies are carried out to assess changes in dopamine-related genes e.g. D2 receptor and dopamine transporter (DAT), glutamate receptor subunits, and inflammatory markers. These studies reduce concern about the significance of the drug's effects and hasten the identification of a drug that targets neurochemical pathways involved in schizophrenia. For example, alterations in dopaminergic signalling are in support of the dopamine hypothesis of Arvid Carlsson. Histopathological examination using the brain's prefrontal cortex and hippocampus to evaluate neuron density, structural integrity and inflammatory change. Neuroprotective effects, lowering of oxidative stress indicators and normalising the structure of the brain architecture point to long-term therapeutic potential. Thus, molecular and histological assessments contribute to the enhancement of the translational validity of the animal model by linking improvements in behavior and biology.

VALIDITY FACTORS OF ANIMAL MODELS

The usefulness of animal models in antipsychotic research depends upon their scientific validity. Since schizophrenia is a complex disorder, there are not enough single model which can replicated all of the features. Therefore, the models are evaluated based on three major criteria of validity: face validity, construct validity, and predictive validity. Face validity is the extent to which the behavioural features of the animal model resemble the symptoms of schizophrenia. For instance, hyperlocomotion induced by amphetamine is mimicking positive symptoms, while social withdrawal and prepulse inhibition (PPI) deficits are negative and cognitive symptoms. Construct validity addresses whether the model's underlying biological processes are similar to the biological processes in human schizophrenia. Dopamine-based models support the dopamine hypothesis proposed by Arvid Carlsson, while models based on the use of the antagonist of the N-methyl D-Aspartate receptor (NMDA) Phencyclidine supports the concept of glutamatergic dysfunction. Predictive validity is the determination of whether or not the model is responsive to clinically effective antipsychotics. Drugs like Haloperidol and Clozapine reliably reverse psychosis like behaviors using validated models.

ADVANTAGES OF ANIMAL MODELS

- Understanding Pathophysiology

- Assessment of Efficacy of Antipsychotics.
- Safety and Toxicity Assessment.
- Controlled Experimental Control.
- Test of Oxidative Stress and Neuro Protection.
- Neurodevelopmental Mechanisms Study.

LIMITATION OF ANIMAL MODELS

- Ineffective modelling of Schizophrenia.
- Minimal Negative and Cognitive Symptom Predictive Validity.
- Centralized Bias in Drug Development Dopamine-Centered Bias.
- Translational Gap and Species Differences.
- Ethical and Welfare Issues.
- Clinical Trials are characterised by high rates of failure.

ETHICAL CONSIDERATIONS

Animal models are instrumental in preclinical research for antipsychotic drugs, however, there is some concern about the ethical use of animal models. Ethical principles must be strictly adhered to in order to ensure humane treatment of animals and scientific validity of results. All the experimental procedures must be in accordance with guidelines laid down by the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), India and also agreed by the Institutional Animal Ethics Committee (IAEC) before commencing the study The 3R principles globally accepted, Replacement, Reduction and Refinement, are to be followed Proper housing, anesthesia, humane handling, and approved euthanasia procedures are mandatory.

CONCLUSION

Preclinical animal models are basic in antipsychotic drugs development, because schizophrenia has complex dopaminergic, glutamatergic and neurodevelopmental mechanisms. Although no one model is entirely capable of replicating the disorder, various types of models, including pharmacological, genetic, and neurodevelopmental models, are combined to simulate the positive, negative, and cognitive symptoms of the disorder. Behavioral tests such as conditioned avoidance response, prepulse inhibition and catalepsy can be part of the drug efficacy and side-effect profile evaluation. Thus a continued need for animal models for the development of safer and more effective antipsychotic therapies.

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