Review Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

https://doi.org/10.36673/AJPCR.2026.v14.i01.A01

PRECLINICAL MODELS FOR EVALUATING CENTRAL NERVOUS SYSTEM-ACTIVE DRUGS: A COMPREHENSIVE REVIEW

Anupriya Thomas*[1], S. Aiswarya[1], P. M. Aswin[1], N. A. Rifa Fathima[1], Z. Shanoop[1]

[1*]Department of Pharmacology, Ahalia School of Pharmacy, Palakkad, Kerala, India.

ABSTRACT

The central nervous system (CNS) governs essential physiological processes including cognition, emotion, motor coordination and behavior. Disorders affecting the central nervous system represent a significant global health burden, necessitating the development of effective and safe pharmacological interventions. Preclinical evaluation plays a crucial role in central nervous system discovery by enabling the assessment of therapeutic efficacy, safety and mechanisms of action before clinical translation. Various experimental models have been developed to study central nervous system pharmacology, including behavioral paradigms and seizure models. This review summarizes widely used preclinical models such as the Open Field Test, Elevated Plus Maze, Rotarod Test, Morris Water Maze, pentylenetetrazole-induced seizures and maximal electroshock-induced seizures, highlighting their applications, advantages and limitations in central nervous system drug development[1-3].

KEYWORDS

Central nervous system, Emerging technologies and Active drugs.

Author for Correspondence:

Anupriya Thomas,

Department of Pharmacology,

Ahalia School of Pharmacy,

Palakkad, Kerala, India.

Email: thomaspd10@gmail.com

INTRODUCTION

The central nervous system (CNS), consisting of the brain and spinal cord, plays a vital role in integrating sensory input, regulating motor output and controlling higher cognitive and emotional functions. central nervous system disorders such as epilepsy, anxiety, depression, Parkinson's disease and Alzheimer's disease are associated with significant morbidity and mortality worldwide[1,4]. Despite advances in neuroscience and molecular pharmacology, the development of effective central nervous system therapeutics remains challenging due to the complexity of neural networks and limitations in translating preclinical findings to clinical success[5].

Preclinical models are essential tools for understanding disease mechanisms and evaluating the safety and efficacy of central nervous system-active drugs before human trials. Animal-based behavioral and seizure models continue to serve as the foundation of central nervous system drug discovery due to their ability to mimic key features of human neurological disorders[3,6].

Importance of Preclinical Evaluation of central nervous system Drugs

Drugs acting on the central nervous system are used to treat a wide range of neurological and psychiatric conditions, including schizophrenia, epilepsy, depression and neurodegenerative diseases[1,2]. However, these drugs may produce adverse effects such as sedation, motor impairment, cognitive dysfunction, tolerance and dependence. Therefore, preclinical evaluation is critical for identifying therapeutic benefits while minimizing safety risks[3].

Key objectives of preclinical central nervous system drug evaluation include assessment of therapeutic efficacy, neurobehavioral safety, neurotoxicity and pharmacokinetic-pharmacodynamic relationships[2,7]. Robust experimental models enhance translational predictability and reduce attrition during clinical development.

Experimental Models Used in central nervous system Drug Evaluation

Animal Models in central nervous system Research

Animal models play a central role in central nervous system research by allowing investigation of complex neurobiological processes that cannot be adequately replicated *in vitro*. Rodents, particularly rats and mice, are the most commonly used species due to their genetic similarity to humans, ease of handling and availability of standardized behavioral assays[4,6]. Animal models have contributed significantly to understanding disease mechanisms in stroke, Parkinson's disease, epilepsy and neurodegeneration[4-8].

Despite ethical concerns and interspecies differences, animal models remain indispensable for evaluating whole-organism responses to central nervous system-active drugs[3].

***In vivo* Models**

In vivo models enable the assessment of drug effects on the intact central nervous system, providing information on pharmacokinetics, pharmacodynamics, efficacy and toxicity. These models capture complex interactions between neural circuits, neurotransmitter systems and peripheral organs[3,7]. However, high costs, ethical considerations and translational limitations must be carefully addressed.

***In vitro* Models**

In vitro models utilize isolated cells or tissues under controlled laboratory conditions and are useful for mechanistic studies and early-stage drug screening. These models offer advantages such as reduced cost, high reproducibility and ethical acceptability[7]. Nevertheless, they lack the physiological complexity of intact organisms and are best used in combination with *in vivo* approaches.

Behavioral Models for central nervous system Drug Evaluation

Open Field Test

The Open Field Test (OFT) is widely employed to assess locomotor activity, exploratory behavior, and anxiety-like responses in rodents. The test is based on the natural conflict between exploratory drive and fear of open spaces. Parameters such as total distance traveled, rearing behavior, and time spent in central versus peripheral zones are commonly analyzed[9-11]. The OFT is frequently used to screen anxiolytic, anxiogenic, sedative, and stimulant compounds[12,13].

Elevated Plus Maze

The Elevated Plus Maze (EPM) is a validated model for evaluating anxiety-related behavior in rodents. It exploits rodents' aversion to open and elevated spaces, with anxiolytic drugs increasing open-arm exploration and anxiogenic drugs producing the opposite effect[12,14]. Although locomotor activity may influence outcomes, the EPM remains a reliable screening tool for anxiety-related pharmacological studies[15].

Rotarod Test

The Rotarod Test is commonly used to evaluate motor coordination, balance and muscle strength. It

is particularly valuable for assessing neurotoxicity and motor impairment induced by central nervous system-active drugs or neurological disorders. Reduced latency to fall from the rotating rod indicates compromised motor performance[16]. This test is widely applied in studies involving neurodegeneration, traumatic brain injury, and sedative drugs[15,16].

Morris Water Maze

The Morris Water Maze (MWM) is a well-established paradigm for evaluating spatial learning and memory in rodents. Animals learn to locate a hidden platform using external visual cues, and performance is measured by escape latency and time spent in the target quadrant[17]. The MWM is extensively used in studies of cognitive enhancers and neurodegenerative disorders such as Alzheimer's disease[18].

Seizure Models in Antiepileptic Drug Screening

Pentylenetetrazole-Induced Seizure Model

The pentylenetetrazole (PTZ) model is a chemically induced seizure paradigm used to assess compounds that increase seizure threshold. PTZ acts as a GABA receptor antagonist and induces clonic and myoclonic seizures resembling absence epilepsy in humans[19-22]. Drugs enhancing GABAergineuro transmission demonstrate protective effects in this model, making it valuable for screening antiepileptic agents[23].

Maximal Electroshock-Induced Seizure Model

The Maximal Electroshock Seizure (MES) model is a widely used experimental paradigm for identifying drugs that prevent seizure propagation. It mimics generalized tonic-clonic seizures and is highly predictive of clinical efficacy[23]. Suppression of tonic hind limb extension is considered an indicator of anticonvulsant activity. The MES model remains a gold standard in antiepileptic drug discovery[19,23].

Recent Advances and Emerging Trends

Recent advancements in automated behavioral tracking, artificial intelligence-based analysis and neuroimaging have significantly improved the sensitivity and reproducibility of central nervous system drug evaluation. Emerging approaches such as brain organoids, computational modeling and machine learning-assisted phenotyping offer promising opportunities to enhance translational relevance and reduce dependence on animal models[7,20].

CONCLUSION

Preclinical models are indispensable for evaluating central nervous system-active drugs. Behavioral and seizure models provide critical insights into therapeutic efficacy, safety and mechanisms of action. Integrating *in vivo, in vitro* and emerging technologies improves predictive validity and supports the development of safer and more effective central nervous system therapeutics. Continued refinement of these models will play a crucial role in advancing central nervous system drug discovery.

ACKNOWLEDGMENT

The authors wish to express their sincere gratitude to Department of Pharmacology, Ahalia School of Pharmacy, Palakkad, Kerala, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Rang H P. Rang and Dale's pharmacology, *Elsevier*, 9th Edition, 2020, 808.
2. Sharma H L. Principles of pharmacology, *Par Med Pub, Hyder*, 2nd Edition, 2023, 1064.
3. National Research Council. Guide for the care and use of laboratory animals, *National Academies Press, Washington (DC)*, 8th Edition, 2011, 1-246.
4. Carmichael S T. Animal models of stroke: size, mechanism and purpose, *NeuroRx*, 2(3), 2005, 396-409.
5. Dunnett S B. Behavioral analysis of motor and non-motor symptoms in rodent models of Parkinson's disease, *Prog Brain Res*, 184, 2010, 35-51.

6. Chesselet M F, Richter F. Modelling of Parkinson's disease in mice, *Lancet Neurol*, 10(12), 2011, 1108-1118.
7. Limb G A. Sixth ARVO/Pfizer ophthalmics research institute conference working group, Current prospects in optic nerve protection and regeneration, *Invest Ophthalmol Vis Sci*, 52(11), 2011, 5941-5954.
8. Wood M D, Kemp S W, Weber C, Borschel G H, Gordon T. Outcome measures of peripheral nerve regeneration, *Ann Anat*, 193(4), 2011, 321-333.
9. Hall C S. Emotional behavior in the rat. III, The relationship between emotionality and ambulatory activity, *J Comp Psychol*, 22(3), 1936, 345-352.
10. Hall C S. Emotional behavior in the rat. IV, The relationship between emotionality and stereotyping of behavior, *J Comp Psychol*, 24(2), 1937, 369-375.
11. Broadhurst P L. Determinants of emotionality in the rat: I, Situational factors, *Br J Psychol*, 48(1), 1957, 1-12.
12. Pellow S, File S E, Briley M. Validation of open: Closed arm entries in an elevated plus-maze as a measure of anxiety in the rat, *J Neurosci Methods*, 14(3), 1985, 149-167.
13. Montgomery K C. The relation between fear induced by novel stimulation and exploratory behavior, *J Comp Physiol Psychol*, 48(4), 1958, 254-260.
14. Barnett S A. The rat: A study in behavior, *University of Chicago Press, Chicago*, 1975.
15. Mouzon B, Chaytow H. Repetitive mild traumatic brain injury in a mouse model produces learning and memory deficits accompanied by histological changes, *J Neurotrauma*, 29(18), 2012, 2761-2773.
16. Jones B J, Roberts D J. The quantitative measurement of motor inco-ordination in naive mice using an accelerating rotarod, *J Pharm Pharmacol*, 20(4), 1968, 302-304.
17. Morris R. Developments of a water-maze procedure for studying spatial learning in the rat, *J Neurosci Methods*, 11(1), 1984, 47-60.
18. Gupta R, Singh M, Sharma A. Neuroprotective effect of piracetam on hypobaric hypoxia induced cognitive impairment in rats, *Indian J Exp Biol*, 40(10), 2002, 1126-1129.
19. Loscher W, Brandt C. Prevention or modification of epileptogenesis after brain insults: Experimental approaches and translational research, *Pharmacol Rev*, 62(4), 2010, 668-700.
20. Loscher W. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs, *Seizure*, 20(5), 2011, 359-368.
21. Loscher W. Animal models of seizures and epilepsy: Past, present and future role for the discovery of antiseizure drugs, *Neurochem Res*, 42(7), 2017, 1871-1888.
22. Kandratavicius L, Balista P A, Lopes-Aguiar C, Ruggiero R N, Umeoka E H, Garcia-Cairasco N, *et al*. Animal models of epilepsy: Use and limitations, *Neuropsychiatr Dis Treat*, 10, 2014, 1693-1705.
23. White H S, Johnson M, Wolf H H, Kupferberg H J. The early identification of anticonvulsant activity: Role of the maximal electroshock and subcutaneous pentylenetetrazol seizure models, *Ital J Neurol Sci*, 16(1-2), 1995, 73-77.
24. Loscher W, Brandt C. Epileptogenesis and its modification in experimental models, *Pharmacol Ther*, 128(3), 2010, 507-534.
25. Pellow S, File S E. Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: A novel test of anxiety in the rat, *Pharmacol Biochem Behav*, 24(3), 1986, 525-529.

Please cite this article in press as: Anupriya Thomas *et al*. Preclinical models for evaluating central nervous system-active drugs: A comprehensive review, *Asian Journal of Phytomedicine and Clinical Research*, 14(1), 2026, 1-4.