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Animal Models for Psychopharmacology - An Overview

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ABSTRACT

Psychopharmacology is the study of drugs, or pharmakon, that affect a person's mind, psyche, and behaviour. A person's thinking, feeling, mood, ability to communicate with others, and daily functioning are all affected by this medical condition. It is a vast and intricate area of medicine that originated with the study of how psychotropic drugs work. Pharmacological mode of action is largely influenced by pharmacodynamic factors. On the other hand, pharmacokinetic factors influence the onset, course, and intensity of pharmacological activity. In all fields of biomedical research, animal models are essential. Despite the long history of utilizing animal models in the examination of neuropsychiatric illnesses and behavioral dysfunctions, the process of animal model design, development, and evaluation has seldom been addressed in a systematic manner. The development and evaluation of animal models is proposed as an iterative, multi-stage process. The first step in the process is to decide what the model's purpose(s) will be, preferably based on theories about the connections between brain and behavior. The model is then created and put to the test. Scientific and moral standards are taken into account in the model's evaluation. The development and evaluation process itself can be improved by carefully defining the purpose(s) of a model and by defining better evaluation criteria, based on the proposed use of the model, in a manner similar to that for improving animal models, guided by the procedure discussed in this paper.

INTRODUCTION:

Psychopharmacology is the scientific study of how drugs affect feeling, sensation, thought, and behaviour [1]. The focus of psychopharmacology is on psychoactive drugs and mental illness as a medically recognized condition. Psychopharmacology is the study of drugs, or pharmakon, that affect a person's mind, psyche, and behaviour. A person's thinking, feeling, mood, ability to interact with others, and daily functioning are all affected by this medical condition. [2, 3]

The signs of mood disarray include distress in the regulation of mood, behaviour, and emotion. Depressive disorders, bipolar disorders, and depression linked to a medical condition are the three groups into which they fall. Severe despair continues to be a group disease that causes significant morbidity and mortality despite significant therapeutic advancements [4]. An estimated 5% of people in the general population experience sadness. There are 121 million people who are probably depressed right now. According to estimates, 5.8% of men and 9.5% of women will experience depression at some point in their lives. Suicide is one of the most common symptoms of depression; the World Health Organization estimates that 450 million people worldwide suffer from emotional or behavioral disorders, but only a small percentage of them will receive even the most basic care. This represents 12.3% of the overall illness overload and will rise to 15% by 2020. [5, 6]

As a result of "an ambitious lifestyle, urbanization, and a stressful environment," mental diseases have become more prevalent. One of the most debilitating, challenging, and expensive conditions is psychosis. "Psychosis is frequently defined as entail a "loss of contact with reality" because the Greek words psyche and osis both mean "mind" or "soul," respectively. These illnesses affect a person's capacity for rational thought, sound judgment, emotional response, effective communication, comprehension of reality, and appropriate behaviour. They are defined by three types of symptoms in general: Symptoms that are positive, negative, or cognitive Positive symptoms include hallucinations, delusions, bizarre behavior, and positive formal thought disorders and signify a loss of reality. [7] Flat affect, alogia, avolition, and anhedonia are examples of negative symptoms that pertain to a reduction or lack of typical activities. Cognitive symptoms include attention, learning, memory, focus, and executive function deficits.

OVERVIEW OF MECHANISMS OF ACTION

The mechanisms of action of psychotropic medicines serve as the foundation for the wide and intricate field of medicine known as psychopharmacology. Pharmacological mode of action is largely influenced by pharmacodynamic factors. On the other side, pharmacokinetic factors influence the onset, course, and intensity of pharmacological activity. [8]

Amphiphilic qualities of psychotropic drugs suggest that they have both hydrophilic and hydrophobic properties. This physical characteristic allows psychotropic medications to easily reach their sites of action. Psychoactive substances either concentrate in the hydrophobic interior of cell membrane lipid bilayers or permeate the plasma membrane (hydrophilic). [9]

NEUROTRANSMITTERS:

In order for a signal to be transmitted, the amount of neurotransmitters in the synaptic space must be optimal, and in mentally healthy people, there is a balance between the amount of neurotransmitters in the synaptic space and in the presynaptic neuron; it is the disruption of this balance that causes mental illness. Neurotransmitters are endogenous chemicals in the human body that are responsible for the transmission of nerve impulses between neurons and target cells across a synapse. The neurotransmitters acetylcholine, serotonin, dopamine, norepinephrine, epinephrine, glutamate, and GABA are a few of the significant ones associated with psychopharmacology. [10]

Acetylcholine:

"Its cholinergic neurons are distributed throughout the CNS, particularly in the brain, where they play a range of tasks including pain perception, neuroendocrine control, REM regulation, and memory and learning development. Acetylcholine is a neurotransmitter that governs muscle movement.

Alzheimer's disease has major cholinergic system pathology. Neurotransmitters like norepinephrine and epinephrine are essential in stress-related diseases because they enable the body to fight or flee in an emergency by speeding up the heartbeat, blood flow, and breathing to meet the muscles' increased oxygen demand. [11]

Dopamine:

Tyrosine is converted to dopamine by the enzymes tyrosine hydroxylase and L-amino acid decarboxylase, and a lack of dopamine in the brain has been associated with the pathophysiology of Parkinson's disease. The same dopamine is overactive in pyschosis (schizophrenia) [5].

Table No. 1: General mechanisms of action of psychoactive drugs

General mechanism of actions of psychotropic drugs	Examples
Synthesis and storage of neurotransmitters	L-Dopa
Release of neurotransmitters from presynapse	Zolpidem, benzodiazepine
Blockade of receptors	Tricyclic antidepressants
Breakdown of neurotransmitters	MAO inhibitors, amphetamines
Reuptake of neurotransmitters	SSRIs
Transduction of G-proteins	Phenothiazines, butyrophenones
Effector system	Antidepressants

PHARMACOLOGICAL TREATMENT OF PSYCHOSIS:

The term "neuroleptic" relates to taking control of one's nerves and is derived from the Greek words "neuroleptic" and "lept," which both mean "to take hold of" and refer to the anti-psychotic medications. Antipsychotic medications work well to treat hallucinations, delusions, and mental problems and are the cornerstone of acute and ongoing treatment for schizophrenia. Antipsychotic drugs are frequently separated into the first generation (typical) and second generation groups. [12, 13] Atypical antipsychotics are classified based on their pharmacological properties, whereas typical antipsychotics are categorized based on their chemical structure. Atypical antipsychotics are typically thought to be more effective and have fewer side effects than traditional antipsychotics, and according to evidence, certain second-generation medicines have less movement-related adverse effects than" first-generation drugs. The main difference between the two types of antipsychotics is that the first-generation medications inhibit dopamine while the second generation meds also impact serotonin levels. [14, 15]

CLASSIFICATION OF PSYCHOTROPIC DRUGS:

In medicine, psychotropic drugs are a class of prescription drugs that primarily treat central nervous system disorders. Whether taken orally or intravenously, psychotropic medications are absorbed by the blood and transported to the brain. They pass through the blood-brain barrier (BBB), a "protective membrane," and enter the brain circulation. [16]

The main goal of these drugs is to cause the desired changes in mood and behaviour to treat and manage psychiatric disorders. Psychotropic "drugs, on the other hand, are formulated especially to cross the BBB and act directly on the brain to alter perception and mood, induce behavioral changes and affect consciousness along with cognition." [17]

Psychotropic medicines are broadly classified as follows:

- “Antipsychotics”
- “Antidepressants”
- “Anxiolytics”
- “Mood stabilizers”
- “Prescription stimulants”
- “Sedative-hypnotics”
- “Miscellaneous drugs (e.g. herbal supplements)”

Antipsychotics:

This "subgroup contains a significant number of drugs used to treat psychosis; psychosis is a generic word that encompasses diseases originating from distorted perception of reality followed by a deficient insight, and Psychotic patients primarily experience these two" qualities.

Antipsychotics "are utilized in the treatment of a wide range of non-psychotic disorders such as Tourette syndrome, autism, and dementia" in addition to mental illnesses like schizophrenia, bipolar disorder, and delusional disorders. [18]

Antidepressants:

A class of medications known as antidepressants is primarily used to treat the signs and symptoms of depressive disorders. Antidepressants, however, have a number of off-label uses, and their use is beneficial for conditions like "anxiety, sleep disorders, obsessive compulsive disorders, eating disorders, neuropathic pain, ADHD, migraines, and drug addiction." [19, 20]

Anxiolytics and sedatives:

As the name suggests, anxiolytics are drugs that are used to relieve anxiety. Monoamine oxidase inhibitors and tricyclic antidepressants also reduce anxiety, but they are rarely advised due to their serious side effects. Barbiturates and benzodiazepines both have "dose-dependent effects on the central nervous system, meaning that the higher the dose, the deeper the sedation-anxiolysis-anesthesia on the CNS, and benzodiazepines are primarily used to treat panic attacks and generalised anxiety disorder."

Stimulants:

Drugs that momentarily elevate mood and enhance both physical and mental function are known as stimulants. They have been widely abused as recreational drugs in addition to being used as prescription medications all over the world. In general, stimulants increase activity in the central and peripheral nerve systems of the brain. They help ADHD patients focus and are used to treat narcolepsy, obesity, excessive appetite, and lethargy.

There are many different types of stimulants, such as ampacines, amphetamine-related compounds, eugeroics, norepinephrine reuptake inhibitors (NERIs), norepinephrine dopamine reuptake inhibitors (NDRIs), xanthine, and caffeine-related drugs. [21, 22, 24]

Sedatives/hypnotics:

Sedatives, also referred to as tranquillizers, are a group of medications that work by preventing the brain's excitatory processes from becoming overexcited. Numerous of the drugs listed above, in particular benzodiazepines, have sedative effects. Barbiturates and antihistamines are examples of sedatives. Because of their dose-dependent effects on the central nervous system (CNS), sedatives are also known as sedative-hypnotics when used before medical procedures. Smaller doses of these drugs may act as anxiolytics, while higher

doses may result in unconsciousness. They are used as a supplement to general anaesthesia and to induce sleep. [23, 24]

ANIMAL MODEL FOR PSYCHOPHARMACOLOGICAL ACTIVITY:

Forced Swimming Test (FST): In 1977, Porsolt and his associates developed the forced swimming test (FST) rat model, which was later applied to conduct behavioral studies on mice. Animals in the FST experience unavoidable stress from having their tails suspended, and as a result, they eventually adopt an immobile posture. The majority of antidepressants can successfully make you move again. For decades, the FST has been used to evaluate a drug's potential as an antidepressant. [25].

This immobility was initially thought to be a sort of desperate behaviour when compared to the worried activity of typical animals. The immobility of FST rodents was later revealed to represent an inhibitory learning behaviour akin to extinction, brought on by the FST's inescapable/unavoidable characteristic. The FST-induced immobility can be thought of as a switch that encourages cognitive functioning for an animal's ability to adapt and survive [26, 27]. However, it has been questioned whether depressive symptoms can manifest as desperate behavior, and recently, some researchers have questioned whether the FST is an effective depression model [28].

The FST's initial design is only one aspect of the controversy. Different rodent species have varying baselines for how they react to antidepressants. For DBA/2 mice, for instance, the FST produces unfavorable results, making it impossible to assess them using this method. The ddY mice have a longer swimming range than other mouse species. Additionally, errors in results could be caused by animals' primary dyskinesia. To get rid of the false depression group that mobility restriction creates, the open-field test (OFT) must be used beforehand [29].

Interleukin-6 and IL-15 levels in the serum can be used to diagnose depression in animals and offer a fresh approach to treating the condition. The FST has been the primary test for assessing modelling and drug-therapeutic efficacy for the past three years. The low statistical power for clinical applications, which might not give a direction for meta-analyses, was the main issue with the studied drugs, which included fluoxetine, tipepidine, and tramadol [30].

The FST has the following benefits: (1) it is a quick, low-cost method that uses a lot of different compounds [28]; (2) it is highly automated, making it a useful tool for testing a

model group; and (3) it is a broad-spectrum method for evaluating the effectiveness of antidepressants with high predictive validity.

The FST has several drawbacks, including the following: (1) a high mortality rate; (2) an inability to assess the etiologic mechanism of depression in both animals and humans; and (3) too many environmental interruption factors to accurately measure the forced swimming test's immobility time.

The FST and OFT are popular behavioural test methods for choosing antidepressants despite the fact that they cannot be used to conduct etiologic investigations [31]. This is because of their high efficacy.

Tail Suspension Test (TST):

The tail suspension test (TST), which was first proposed by Steru and colleagues in 1985, exhibits an immobile posture and uses a similar depression induction mechanism to the FST. Similar findings were made regarding the TST's suitability for identifying an animal's "desperate attitude." Instead, it is useful for identifying a copy or survival-based change in behaviour from active to passive brought on by intolerable environmental stress [32].

Antidepressants that break this immobility and encourage behaviour of escape can be viewed as therapeutic drugs. However, when an antidepressant intervention is used, the dose-response curve of these two behavioural tests differs [33].Additionally, different rodent species have varied baselines for how long they are immobile for. For instance, whereas this phenomenon does not occur in C57BL/6 mice, the immobility time of Swiss mice in the TST is seven minutes shorter than that in the FST [34]. It can be seen as a veiled illustration of the need to confirm the construct's validity. Typical or atypical antidepressants, such as SSRIs and monoamine oxidase (MAO) inhibitors, can shorten the immobility period. For instance, nimodipine can mimic the effects of an antidepressant by disrupting the MAO-B receptor by forming liposomes [35].

The TST has the following benefits: (1) it can simultaneously assess the effectiveness of antidepressants in a variety of model animals; (2) it requires little money and labor; (3) it can supplement the FST (in some circumstances, such as hypothermia, the TST can take the place of the FST to quantify animal behaviors); and (4) it can be used with mice and rats. The TST, which poses just a slight risk to animals compared to the low accuracy of the FST, can be viewed as a gentle stimulation procedure that is not life-threatening. The TST has a few

drawbacks, including the following: (1) it is an incomplete protocol because it relies on other tests; and (2) the pharmacodynamic effect of antidepressants acts too quickly in the TST to predict the best course of treatment for depressive patients.

Open-Field Test (OFT):

When animals are confined in a completely alien habitat, their early behaviour can reveal their emotional status. The open-field test (OFT) simulates dangerous conditions, assesses animal autonomy, and exposes the level of stress in the animals [43]. Animals typically avoid unfamiliar environments and stay out of the centre of a black box, rarely entering it. However, their innate propensity for making exploratory endeavours will drive them to investigate the core location, allowing researchers to see how depressed the rats are. Investigators can easily spot instances of reduced activity in depressed animals because they run for shorter periods of time when using a three-dimensional (3D) imaging sensor to track the movement of animals [36]. Each rat that is subjected to the OFT should be cleaned off in a previous way for the FST to get rid of any odour that might draw in other rats. The antidepressants that are frequently prescribed have therapeutic effects on rats in the OFT.

The following are some of the benefits of the OFT: It is superior to other tests in five ways: (1) it is more efficient and practical due to its semi-automatic operation (similar to the FST); (2) it causes less harm to animals; (3) it is highly predictive of therapeutic similarity; (4) it is excellent for measuring fear and despair; and (5) it serves a dual purpose by being used to test anxiety-like animal models.

The following are the OFT's drawbacks: (1) it is time-consuming; (2) it has low construct validity for the investigation of etiology; and (3) it is sensitive to alterations in the environment.

Sucrose Preference Test (SPT):

Anhedonia, or a lowered capacity for happiness, is frequently assessed in animals using the sucrose preference test [37]. A decrease in an experimental animal's sucrose consumption ratio is a sign of an effective depression model with anhedonia. The SPT is regarded as the most suitable behavioral test for the chronic moderate stress scenario. An exceedingly severe depressive state is typically indicated by two internal phenotypes in psychopathology: anhedonia and pressure sensitivity. It also symbolises a state of exhaustion or loss of energy brought on by mental stress, which antidepressants can treat. In terms of the method for

calculating the ratio of water consumption to sucrose solution ingestion, a decreased intake of sucrose signifies that an animal is in a depressed state.

The advantages of this test are: (1) it is the most convenient test for anhedonia in depressed animals; (2) it results in less harm to animals; and (3) it is suitable for use in studies on the comorbidity of depression and pain. [38, 39]

The disadvantages of this test are as follows: (1) it is a time-consuming test that takes three days to prepare; and (2) it is too rough to accurately indicate the depressive state of animals.

Other Behavioral Tests:

The hyponeophagia-based novelty-suppressed feeding (NSF) test offers a sensitive paradigm for evaluating the effectiveness of antidepressants [40]. The NSF's primary factors are the amount of food consumed and the latency duration between meals. As an animal model for examining the neurological facets of antidepressant effects, this test shows some benefits [41]. For instance, the NSF creates a situation where animals are motivated to feed while also being afraid to enter the centre of an open space with an extremely bright light. These two antagonistic conditions have excellent construct validity for researching an anxious mood during an antidepressant treatment course. Researchers have the chance to examine the relationship between a neural circuit and an antidepressant effect since the NSF test's latency is causally linked to the hippocampus's neurogenesis function [40]. The NSF test's biggest drawback is that it cannot be administered alongside other behavioral tests at the same time.

The elevated plus maze (EPM) test, which is somewhat similar to the OFT in that it focuses on the anxiolytic effect on animals, was developed [41]. When used in conjunction with the OFT test, the EPM test may be a useful tool for evaluating changes in anxiety behaviour because depression is frequently accompanied by anxiety [42, 43, 44]. Major depressive disorder has also been linked to cognitive deficits. Thus, a cognitive test, such as the spontaneous alternation test, can also be performed on a depressed animal [45, 46].

CONCLUSION:

Unfortunately, there is no agreement on the importance or priority of the several stages that must be taken in order to build an animal model, and there are no universally recognized standards for assessing the resultant putative model. The scientists may be guided through the model building and model evaluation process if they view model creation as an iterative,

multi-step process with an evaluation stage and predefined appraisal criteria. Animal models for use in other types of research can also be developed and/or assessed using the described approach. The development and evaluation process itself may be improved by carefully defining the purpose(s) of a model and by defining better evaluation criteria, in a manner similar to how animal models can be improved under the guidance of the above-described procedure.

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