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Animal Experimental Models Used in The Study of Psychiatric Diseases

Psikiyatrik Hastalıkların Araştırılmasında Kullanılan Hayvan Deneyi Modelleri

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Abstract

Animal experimental models used for modelling psychiatric diseases and treatments are an indispensable tool. But it is impossible to construct a single animal model which demonstrates every aspect of a psychiatric disease. Thus, partial models are preferred. The validity of models is examined for construct, face and prediction dimensions. This evaluation is used together with the similarity with human disease and is of vital importance in terms of obtaining findings that will contribute to clinical applications. Learned helplessness, forced swim tests and tail suspension test are traditional tools for modelling depression with good predictive but limited construct validity so research shifted away from them. In depression research, animal models focusing on basic formations such as anhedonia comes to the fore. Chronic mild stress (CMS) protocol is used to create anhedonia and dependent variables like sucrose preference, intracranial self-stimulation reward (ICSS) and progressive ratio reward are used to measure the anhedonia with good face and predictive validity. Anxiety models include high plus maze, operant conflict test and social interaction paradigms best used to determine drugs anxiolytic effects. Modeling schizophrenia is challenging because of the complexity of positive, negative, and cognitive symptoms that make the disease a uniquely human thought disorder. Pharmacological manipulations like dopaminergic or glutamatergic agents, neonatal brain lesion models, and genetic manipulation techniques have been developed in this area. Prepulse inhibition (PPI), latent inhibition, and working memory tests, while not fully valid, provide results similar to humans. Addiction research utilizes animal models that reflect the stages of binge/intoxication, withdrawal, and craving. Measurements of intracranial self-stimulation threshold (ICSS) measurements, conditioned place preference (CPP), and stress-induced reinstatement are used to demonstrate how substance use escalates, how reward thresholds change, and why relapse occurs. These methods demonstrate strong predictive validity and provide experimental settings for testing new pharmacological interventions. In general, animal models provide an irreplaceable opportunity for investigating the neurobiological and behavioral mechanisms for psychiatric illness. Despite their partial validity, these models are indispensable for investigating etiology, identifying therapeutic targets, and guiding clinical research. Future studies with improved model designs and incorporating genetic and environmental factors will increase the applicability to complex psychiatric conditions.

Keywords: Animal Models, Psychiatry, Schizophrenia Models, Depression Models, Addiction Animal Models.

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Öz

Hayvan modelleri, psikiyatrik bozuklukların oluşumunu anlamada ve deneysel müdahaleler yapmada önemli rol oynamaktadır. Ancak psikiyatrik hastalıkların tüm klinik özelliklerini hayvanlarda sergileyen kapsamlı modeller oluşturmak mümkün değildir. Bunun yerine, araştırmalarda depresyon, anksiyete, şizofreni ve bağımlılık gibi bozuklukların belirli semptom kümelerine odaklanan kısmi modeller kullanılmaktadır. Depresyon araştırmalarında hayvan deneyleri kronik hafif stres paradigmasıyla modellenir. Bu modelde depresyonun bağımlı değişkenleri ise intrakraniyal öz uyarım, sakkaroz tercihi ve progresif oranlı pekiştireç tepkisi ölçümleridir. Her değişken geçerlilik ve güvenilirlik açısından farklılık gösterse de, anhedoni ve motivasyonel eksiklikler hakkında geçerli ölçümler sunar. Anksiyete modellerinde ölçümler; yükseltilmiş artı labirent, operant çatışma testi ve sosyal etkileşim değerlendirmeleri gibi testler aracılığıyla gerçekleştirilir. Sıklıkla ilaçların anksiyolitik etkilerini belirlemede kullanılırlar. Ancak bu ölçümler genellikle panik bozukluk veya PTSD gibi belirli alt tipler yerine yalnızca yaygın anksiyeteyi yansıtır. Şizofreniyi modellemek, hastalığın insana özgü bir düşünce bozukluğu olması dolayısıyla; pozitif, negatif ve bilişsel semptomların karmaşıklığı nedeniyle güçtür. Bu alanda farmakolojik manipülasyonlar (örn.; dopaminerjik veya glutamaterjik ajanlar), neonatal beyin lezyonu modelleri ve genetik yaklaşımlar geliştirilmiştir. Prepulse inhibisyon, latent inhibisyon ve çalışma belleği testleri, tam görünüş geçerliliği sunmamakla birlikte insanlardaki bulgulara benzer sonuçlar sunmaktadır. Bağımlılık araştırmaları, aşırı tüketim/entoksikasyon, yoksunluk ve aşerme evrelerini yansıtan hayvan modellerinden faydalanır. İntrakranyel self stimülasyon eşik ölçümleri, şartlandırılmış yer tercihi ve stres kaynaklı yeniden madde arayışı gibi ölçümler, madde kullanımının nasıl arttığını, ödül eşiklerinin nasıl değiştiğini ve nüksetmenin neden meydana geldiğini göstermede kullanılır. Bu yöntemler güçlü prediktif geçerlilik gösterir ve yeni farmakolojik müdahaleleri test etmek için deney ortamı sağlar. Genel olarak, hayvan modelleri psikiyatrik hastalıkların altında yatan nörobiyolojik ve davranışsal mekanizmalara ışık tutmada yeri doldurulamaz bir alan sunar. Bu modeller geçerliliklerinin kısmi olmasına rağmen; hastalık etyolojisini araştırmak, terapötik hedefleri belirlemek ve klinik araştırmalara rehberlik etmek için elimizdeki iyi birer araçtır. Model tasarımlarını iyileştirerek ve genetik ve çevresel faktörleri entegre ederek; gelecekteki çalışmalar bu modellerin karmaşık psikiyatrik durumlara uygulanabilme gücünü artıracaktır.

Anahtar Kelimeler: Psikiyatride Hayvan Modelleri, Bağımlılık Modelleri, Şizofreni Modelleri, Depresyon Modelleri.

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Introduction

Animal Experimental Models Used in The Study of Psychiatric Diseases

Animal Model Definitions Associated with Psychiatric Disorders

Animal models are experimental paradigms developed to study specific phenomena observed in humans. Complete animal models encompassing the entire syndrome of psychiatric disorders are conceptually or practically impossible. Although there is no single animal model that reflects the entire clinical picture of the syndrome in the case of addiction, anxiety, or depression, there are partial models that focus on specific elements of these disorders (1). Incorporating issues such as comorbidity, polysubstance use, and child abuse into animal studies is also challenging.

The fact that psychiatric disorders are defined on the basis of a complex and ever-changing classification and include many subtypes and different etiologies makes holistic models difficult in practice. Therefore, approaches that model only certain symptoms of the disorder may be more useful in terms of face, construct and predictive validity (1).

Assessing the Validity of Animal Models

Validity of animal models are generally evaluated across three dimensions (Table 1). The most critical concept in animal models in the field of addiction is construct validity. This refers to the interpretability and explanatory power of the animal model; it also looks at whether the model is consistent with different criteria or known conditions. A procedure is considered to be construct valid if it provides meaningful relationships between observable data (e.g., reward threshold) and a theoretical construct (e.g., the concept of reward) (2). In terms of construct validity, the model and the controlling variables are expected to produce similar results in both the model and the target disorder. This is usually tested with common experimental manipulations (3).

Table 1.

Validity assesment aspects of animal models of psychiatric disorders

1. **Construct Validity:**
    - The degree to which the model reflects the basic biological, genetic or neurophysiological processes of the psychopathological condition in question is evaluated
2. **Predictive Validity:**
    - It is examined whether the animal model responds to the same treatment methods or drugs that are effective in humans. For example, an antidepressant used in a depression model is expected to be effective.
3. **Face Validity:**
    - It is assessed whether the model exhibits behavioral or physiological characteristics similar to symptoms seen in humans. For example, in anxiety models, the presence of fear or avoidance behaviors is important.

Face validity is based on the similarity of animal syndromes to human conditions, but mimicking all human symptoms is usually limited (4). Predictive validity is assessed by the capacity of the model to make accurate predictions about the clinical condition (4).

Animal Models of Depression: Measurements of Reward and Motivation

Introduction and Definitions

Depression is a common and important public health problem and risk factors include genetic and stress-related factors. Traditional animal models used to assess the efficacy of antidepressant drugs consist of a series

of tests that offer high efficiency and ease of use. These tests include antagonism of reserpine-induced behavioral changes (depletion of dopamine, serotonin, and norepinephrine) and potentiation of the effects of substances such as tryptophan(serotonin), apomorphine(dopamine), or yohimbine(norepinephrine) with behavioral measures such as the forced swim test. Such tests are widely used to study the mechanisms of action of antidepressant drugs.

In non-pharmacological depression modeling approaches; various models such as forced swim test, learned helplessness, olfactory bulbectomy have been traditionally used. Today, there is a tendency towards "endophenotype-like" criteria rather than these broad models. Modeling of core depressive symptoms such as reward deprivation(anhedonia) has gained importance due its excellent validity across all three dimentions. Chronic mild stress (CMS) is frequently used to examine the impairment in reward motivation. Here, the main dependent variables are sucrose consumption/preference, intracranial self-stimulation reward (ICSS), and progressive ratio reinforcement for natural reward.

Chronic Mild Stress: A Model for Depression

Rats are exposed to various mild stressors such as they deprived of food and water, constant lighting, tilted cages, cold environment, noise or stroboscopic light for 5–6 weeks. As a result, symptoms associated with depression such as decreased sexual behavior, sleep disturbances, immune and HPA axis dysregulation are observed. Below are the measurement tools to examine depression induced by the chronic mild stress in animals (5) (Table 2).

Table 2.

Behavioral Assessments for Depression in Animals

- Intracranial Stimulation Award (ICSS)
- Sucrose Intake/Preference
- Progressive Ratio Reward

Intracranial Stimulation reward (ICSS)

ICSS offers several advantages over natural rewards: It directly stimulates reward circuits and the extent to which the subject rewards himself can be measured directly (frequency or current intensity). In animals subjected to chronic mild stress, an increase in threshold values in the ventral tegmental area (i.e., a decrease in reward sensitivity) has been observed. The use of antidepressants for 14-21 days can reverse the depressive-like state by lowering this threshold again (5).

Sucrose Intake/Preference

Sucrose is a naturally rewarding substance for rodents. A decrease in sucrose preference is seen as a reflection of anhedonia. In rats with chronic mild stress, sucrose preference typically decreases. This can reversed by antidepressant drug treatment (5).

Progressive Ratio Reward

This method is used to measure the "relative strength" or motivational value of a reward. It does not always give consistent results in the chronic mild stress model; sometimes the response rate does not change or may even increase. In contrast, when depression is modeled with psychostimulant withdrawal, a significant decrease in progressive rate responding is seen (6).

Validity of Animal Models of Depression

As can be seen, the three measures of reward deprivation discussed in this review differ significantly in terms of sensitivity, reliability, and construct validity. Brain stimulation reward provides a reliable and sensitive method for measuring reward deprivation that occurs in substance withdrawal, consistent with reward deprivation described in humans. Neuropharmacological validation of brain stimulation reward has shown that agents that lower thresholds increase reward value in humans, whereas agents that raise thresholds generally elicit dysphoric responses in humans, supporting construct validity (5). With more limited data,

progressive ratio rewarding appears to produce reductions in thresholds for natural rewards associated with substance abstinence, which is consistent with data on brain reward thresholds (7).

However, the sucrose preference model, although widely used, is much less reliable and valid. While some studies associates decrease in consumption with weight loss, others contradict (8). Decreases in sucrose consumption are often not observed during substance abstinence or at all in humans. As a result, many studies have found no changes in sucrose consumption and/or preferences. In fact, humans experiencing episodes of major depression report an increased "craving" for sweets, the opposite of rats exposed to chronic mild stress. However, sucrose consumption after chronic mild stress has predictive validity for antidepressant treatments, which is one reason why sucrose consumption/preferences are increasingly popular in the literature (8). Another reason for the widespread use of sucrose consumption/preference is probably that it is easier to measure.

Anxiety Animal Models

Introduction

Anxiety can be an adaptive emotion in the face of threat, but it can also be disabling when it becomes excessive. Clinically, subtypes such as generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) have been identified. Most animal models aim to examine specific anxiety-like states rather than reflect the full range of symptoms in humans.

Animal Models of Generalized Anxiety Disorder

Animal models of anxiety disorders are listed in Table 3.

Table 3.
Animal Models of Anxiety

Operant Conflict Test
Elevated Plus Maze
Defensive Retreat
Defensive Embedding
Social Interaction
CO_2 inhalation
Schedule-induced polydipsia

Operant Conflict Test

In this widely used test, positive reinforcement (food, water) is sometimes combined with punishing stimuli (electric shock). For example, the Geller-Seifter test (9) and the Vogel conflict test (10) are frequently used. They exhibit high specificity in detecting anxiolytic drugs that target the GABA receptor. However, training for these tests takes time and factors such as the effect of the drug on feeding motivation cannot always be clearly separated (8).

Elevated Plus Maze

It is a plus-shaped maze platform usually 50 cm above the ground. Closed Arms are surrounded by high walls and give the animals a sense of a safer space (11). Open arms have no borders and the feeling of being in an open space can increase anxiety (11). The test assumes that animals naturally experience a conflict between curiosity about new environments and seeking safety.

GABA agonists generally increase exploration in open arms, whereas inverse agonists decrease it. It is popular because it is easy to administer, but it may not always reflect specific types of anxiety such as panic (8).

Defensive Retreat

The time the animal hides in a dark compartment placed in a bright area is recorded. Benzodiazepines shorten the hiding time; adrenergic drugs may increase it. It is thought to reflect agoraphobia. In addition, the effects of CRF agonists/antagonists can be examined in this model and the stress response can be evaluated.

Defensive Burying

It is a test based on rodents burying objects they consider disturbing in sawdust. Benzodiazepines reduce this behavior, and CRF can strengthen it. Similar behavior can be triggered with neutral objects (e.g. glass marbles) (12). It has been suggested that this test has face validity for specific phobias or obsessive-compulsive traits (13).

Social Interaction

Here, the duration of mutual social behavior of two male rats (or mice) in a novel environment is measured. High light or novelty suppresses social interaction and increases anxiety-like behavior. GABA agonists, opioids, and some serotonergic drugs can increase social interaction in a bright environment. Antidepressants are generally ineffective (except for long-term use) (14).

Animal Models of Other Anxiety Disorders

There is no single model with general validity for panic disorder, obsessive-compulsive disorder, and PTSD. Panic attacks can be modeled in rats by CO2 inhalation or lactate, CCK-4 or doxapram infusion. Since panic disorder also include fear of panic attacks with avoidance panic related cues; Vogel conflict test (10) can be used to measure anxiety and this model may reflect CO2-induced panic symptoms in humans. However, unlike humans' rodents do not voluntarily inhale CO2 deeply, so mechanical lung applications on rodents may be a solution for a better panic disorder model.

One proposed model for obsessive-compulsive disorder is "schedule-induced polydipsia," observed in rats exposed to intermittent food intake. Food offered in small amounts and at intervals triggers excessive drinking behavior in response to hunger stimuli. SSRIs reduce excessive drinking after 14–21 days. However, benzodiazepines may increase this behavior, while CRF may decrease it (12), which may have results that may be inconsistent with OCD (13).

Protocols that include various repeated shocks, developed for PTSD but there is no specific pharmacological treatment the biological pathomechanisms of PTSD are still far from being understood, so it is difficult to define exact conditions of construct validity (15).

Validity of Animal Models of Anxiety

Many of these models are aimed at identifying effective drugs for generalized anxiety disorder and have good predictive and face validity in this direction. On the other hand, additional models are needed for panic disorder, OCD, phobia, and PTSD. The lack of pharmacological treatments, especially in the areas of PTSD and specific phobia, makes model development even more difficult.

Another limiting factor is that anxiety requiring treatment in the clinic is seen in patients with high "trait anxiety", whereas animal tests are based on the "state anxiety" (16). Nevertheless, these tests can be considered valid to the extent that they reflect clinical pathology. Genetically high anxiety animal lines or genetic manipulations may allow this distinction to be examined more clearly in the future.

It is also difficult to distinguish different anxiety subtypes in animal models (16). In the case of panic disorder and generalized anxiety disorder, it is not clear whether the two syndromes have separate biological bases (8). While the high-concentration CO2 inhalation test has been used in the differential diagnosis of panic disorder and generalized anxiety disorder in humans, it loses its reliability because rodents do not voluntarily inhale CO2 deeply. More valid panic disorder models can be developed by overcoming this limitation through an alternative method such as the use of a mechanical lung. Factor analysis can separate the behavioral measurements into basic factors such as "anxiety," "exploration," and "locomotor activity" (16).

Schizophrenia

Schizophrenia has been considered very difficult to model in animals due to the human-specific aspects of thought, perception, and language. Currently, classifications offer consensual criteria for a set of possibly overlapping disorders (17, 18). In this framework, schizophrenia includes three main symptom clusters:(1) Negative symptoms (social withdrawal, alogia, apathy, restricted affect), (2) Positive symptoms (hallucinations and delusions), and (3) Cognitive impairments (problems in attention, memory, planning and abstract thinking, disorganization of speech and perception) (17-19). The disease mostly occurs in the 20s; however, prodromal symptoms such as mild sensory, motor and social dysfunctions may be observed at an earlier stage.

Schizophrenia is often considered a neurodevelopmental disorder. What is known about its etiology and pathophysiology is limited, the role of environmental factors (e.g. traumatic life events, substance use, chronic stress) in the development of schizophrenia is remains controversial (20).

All schizophrenia animal models are heuristic tools, due to our incomplete understanding of underlying mechanisms. Pharmacological models disrupt dopaminergic and glutamatergic pathways. Neonatal brain lesion models in rodents aim to mimic developmental brain disorders. Genetic models are based on the manipulation of genes thought to be involved in disease etiology (21).

Behavioral Reflection of Schizophrenia Symptoms

In animal models, not all symptoms of schizophrenia appear simultaneously, as they do in patients (21). In these models, specific behavioral tests are used to investigate how experimental interventions trigger certain symptoms. However, none of the tests are specific to schizophrenia; most are general behavioral paradigms used in other disorders (21).

Cognitive Symptoms

Attention, working memory, executive functions, and declarative memory are frequently impaired in schizophrenia. Since these dysfunctions are not specific to humans, they are easier to study in animals.

Prepulse Inhibition (PPI)

In schizophrenia, patients may not be able to filter sensory information and exposed to excessive stimulation. The PPI paradigm, which regulates the startle reflex, measures the suppression of the response caused by a stronger stimulus by a weaker stimulus. PPI is reduced in schizophrenic patients and in individuals without psychosis who are taking dopamine agonists (22). This impairment can be partially corrected with antipsychotics. Although it is a popular and translational test from an animal model (21), low PPI are not specific nor diagnostic (22).

Latent inhibition

Latent inhibition (LI) is an information filtering concept which refers to reduced attention given to a previously encountered stimulus that was neither important nor reinforcing. Absence of this effect has been linked to the cognitive overload that occurs when patients with schizophrenia pay attention to unimportant stimuli, resulting in an inability to sustain attention. Amphetamine impairs LI in humans (23), whereas antipsychotics enhance it (24). Animal models offer good face and construct validity.

Working Memory and Executive Functions

Working memory is the ability to remember and process information for a short time. Executive functions include higher-level cognitive processes such as planning, decision making, error correction, and attention. These functions are performed by the prefrontal cortex. Impairments on working memory and executive function tests are common in schizophrenia. Working memory and cognitive flexibility can be measured in animal models with tests such as hole-finding, radial arm maze, or Morris water maze (8). Similarly, “attentional set-shifting” tasks have been developed in animals, similar to the Wisconsin Card Sorting Test in humans. Animals with impaired prefrontal cortex function often have difficulty with these “interdimensional attention shift” tests.

Positive Symptoms

It is not possible to directly measure hallucinations or delusions in animals (23). Therefore, "similar" behaviors related to positive symptoms, are examined. For example, increased motor activity (open field test) can be observed in animal models of psychomotor agitation when placed in a new environment. Increased locomotor activity response to psychostimulants can also used as a tool for psychomotor agitation (21).

Negative Symptoms

Ventral hippocampus lesions, DISC1 and NRG1 gene mutations, ketamine infusion and early social isolation are used to create negative symptoms in animals (16). These symptoms can be evaluated using social interaction tests such as the frequency of contact with a stranger, friendly approach and aggressive behavior of the animals (21).

Since the negative symptoms of schizophrenia (anhedonia, social withdrawal, etc.) can also be seen in depression, their association with schizophrenia must be confirmed by demonstrating the ineffectiveness of antidepressant treatments on these symptoms.

Animal Models of Schizophrenia

Animal models of schizophrenia are listed in Table 4.

Table 4.

Behavioral assessments in Schizophrenia Animal Models

Cognitive symptoms
Attention
• Prepulse Inhibition (PPI) • Latent inhibition
Executive functions:
Working memory
• Holeboard • Y-maze • Radial arm maze
Behavioral flexibility
• Extinction of operant behaviors • Morris water maze • Attentional set shift
Positive symptoms
• Open field test • Psychostimulant induced locomotor activity test
Negative symptoms
• Anhedonia • Affective behaviors • Social withdrawal

Pharmacological Models

The first models are based on psychostimulants (amphetamine, methylphenidate) or dopamine agonists(apomorphine) (21). These drugs increase locomotor activity, causing impairments in tests such as PPI and latent inhibition, which are alleviated by antipsychotics (21). It is thought that dopamine excess may be related to the positive symptoms of schizophrenia in particular; however, causal evidence is limited (21).

On the other hand, substances such as NMDA receptor antagonists PCP and ketamine cause psychosis-like symptoms in healthy individuals and increase symptom severity in schizophrenia patients (21). This suggests that glutamate hypofunction may also play a role in schizophrenia. Subchronic PCP administration impairs working memory in animals, which can be partially corrected with atypical antipsychotics (e.g. clozapine) (25). PCP also suppresses social behavior; these effects are more pronounced after chronic use and can be reversed with clozapine, while typical antipsychotics cannot correct this (25).

Neurodevelopmental Models

Epidemiological data have shown that factors such as early pregnancy complications, birth trauma, perinatal hypoxia and prematurity may increase the risk of schizophrenia. In this context, the "neurodevelopmental hypothesis" has been developed. Lipska and Weinberger developed a rat model in which the ventral hippocampus was bilaterally lesioned after in 7th day of life (26). These lesions affect the pathways to the prefrontal cortex, and while normal or mild effects are observed until adolescence, dopaminergic hypersensitivity, increased locomotor response, impaired PPI, working memory deficits and latent inhibition disorders are observed in adulthood (26).

Genetic Models

Human genetic studies have identified many loci and genes thought to be associated with schizophrenia. For example, mutations in the DISC1("disrupted in schizophrenia 1") gene have been linked to certain phenotypes in animals, such as ventricular enlargement and cognitive impairment (27). The G72/G30 locus in the human genome is another candidate; however, these genes may not have an exact counterpart in rodents (8). However, there are studies showing that transgenic mice can exhibit schizophrenia-like behaviors, such as PPI impairment and symptoms that can be improved by antipsychotics (28).

Although schizophrenia is thought to have a hereditary basis, a genomic variant or combination with full penetration has not yet been identified. The fact that the disease is seen in 50% of homozygous twins supports the genetic predisposition, but it also strengthens the view that environmental factors, epigenetic mechanisms, and spontaneous genomic events are at least as effective as genetic factors. In this context, complex gene-environment interactions must also be considered to understand the etiology and pathophysiology of schizophrenia. Although it is not possible to directly examine such interactions in humans, controlled studies on environmental variables can be conducted in modern animal research facilities. Indeed, environmental factors such as urban birth, prenatal viral infections, perinatal oxidative stress, or exposure to cannabinoids during adolescence, which have been shown to affect the rate of schizophrenia in retrospective human studies (29), have also been shown to have significant effects on schizophrenia-related behaviors in rat models (30).

Animal Models of Addiction

Addiction is defined as a disorder ranging from impulsivity to compulsivity and is examined in a three-stage cycle according to DSM-IV criteria:(1) binge/intoxication, (2) withdrawal, and (3) preoccupation/craving (18). Although the first experimental studies in this area focused on the initial positive reinforcement effects of more addictive substances, the primary area of investigation in recent years has been on the motivational changes that develop in the context of addiction (31). Animal models of addiction are listed in Table 5.

Table 5.

Behavioral assessments in animal models of addiction
Intoxication phase
Self-administration
Intracranial self-stimulation (ICSS)
Conditional place preference (CPP)
Drug Discrimination
Genetically selected animal models
Patterns of drug taking despite punishment
Deprivation
Intracranial self-stimulation
Conditioned place aversion
Disrupted operant schedules
Drug discrimination
Measures of anxiety
• Elevated plus maze
• Defensive burying
Preoccupation/Craving
Drug-induced renewal
Cue-induced renewal
Cue induced renewal without extinction (relapse)
Stress-induced renewal
Second Degree Reinforcement Schedules
Protracted abstinence
Conditioned withdrawal

Animal Models of The Intoxication Phase

These models are organized to parallel the DSM-IV addiction criteria for the three stages of addiction (18). For an animal model, it is necessary to objectively define and reliably demonstrate the conditions under which a particular behavior is a symptom of a substance use disorder. Drug reinforcement does not necessarily lead to addiction (e.g., social drinking) because in humans the behavior being modelled can occur in both pathological and normal situations and still have predictive validity. Yet in humans drinking alone has great predictive validity for the binge/intoxication stage of addiction (32), and it is difficult to imagine addiction without drug reinforcement.

Intracranial Stimulation Reward (ICSS) models

As mentioned above in depression models, animals perform a variety of tasks to self-stimulate reward circuts. Drugs of abuse lower ICSS thresholds, and the extent to which drugs reduce ICSS thresholds is strongly correlated with their abuse potential (33).

Conditional Place Preference (CPP) models

CPP is a Pavlovian conditioning paradigm. The animal's preference for environments paired with the drug indicates the positive reinforcement of the substance. Similarly, aversive situations can be measured as place aversion (34).

Drug Discrimination models

In this model, the internal(interoceptive) cues that drugs cause in subjects act as discriminative stimuli that determine which response the animal will give. With this method, it is possible to examine the similarity of a new substance to a known addictive substance with a good predictive validity (35).

Intravenous and Oral Self-administration Models

Animals can learn to self-administer drugs that reward the brain, especially the dopaminergic system, without becoming addicted. Drugs that exhibit positive reinforcement effects, as measured by lowered brain stimulation reward thresholds and conditioned place preference, particularly in models of continuous self-administration, have a large overlap with drugs with high abuse potential in humans. Performance on a progressive ratio schedule can be related to the following principle from the DSM-IV addiction criterion: "Excessive time spent on activities required to obtain the substance" (18). Oral self-administration models are almost always framed around alcohol because of the apparent face validity.

The two-bottle cage drinking option is one of the most widely used paradigms to study ethanol consumption in rodents. In its simplest form, animals are provided access to two water bottles, one containing plain tap water and the other containing ethanol, for 24 hours per day. Daily consumption is measured by the weight change of bottle over a 24-hour period. In this model, the choice of two bottles is sometimes measured by filling both bottles with water and measuring the animal's operant conditioning. In the drinking in the dark model (36), mice can be made to voluntarily consume high doses of alcohol only when alcohol consumption is restricted during day hours. It can be observed that much higher doses of alcohol are consumed as available time is shortened (36).

Genetically Selected Animal Models

In the study, also known as the "Indiana University Rat Lines", high and low alcohol preference strains of rats were genetically selected. The observation that rats in the high alcohol preference strains voluntarily preferred to maintain blood alcohol levels in the range of 50–200 mg% suggests that these rat models have parallels with genetic hypotheses about risky alcohol intake in humans (37).

Patterns of Drug Taking Despite Punishment

In addiction, compulsive use is prominent. In some models, aversive stimuli given simultaneously with the drug reduce substance seeking in non-addicted animals, but seeking is not suppressed in animals with long-term drug intake (38).

Summary of Animal Models of the Intoxication Phase

These methods are reliable tools for understanding the neurobiological basis of acute reinforcing effects and compulsive substance-seeking behaviors during the intoxication phase of the addiction cycle. Although substance addiction is suggested to involve maladaptive mechanisms that go beyond the short-term effects of drugs, examination of positive reinforcing effects provides an important framework for understanding the long-term effects of these mechanisms on motivation.

Drug use disorder is a disease that progresses with periods of intense use and the preferred substance can change. An advantage of intoxication phase models is that they are suitable for designing different operant models with a trained animal. Tests can be performed with the same subject for weeks and dose-effect analyses can be created for different substances. In addition, results can be verified by applying pharmacological manipulations with standard reference compounds (35).

The advantage of the ICSS measurement for studying substance effects on motivation and reward is that behavioral threshold measurements are quantitative (across stimulus frequency and duration) and consistent

over long periods of time. Furthermore, the ICSS technique has high specificity in predicting the abuse potential of drugs; no false-positive results have been recorded to date.

The conditioned place preference (CPP) model stands out with its high sensitivity to low doses, suitability for examining positive and negative reinforcement effects, and allowing drug effects to be tested in sober conditions.

Models such as drug taking despite punishment with progressive ratio schedules have face and construct validity. Literature shows that individuals who meet addiction criteria exert more effort to obtain the substance and their behavioral repertoire narrows around substance seeking and use (18). In rat models of drug seeking despite punishment and progressive ratio paradigms suggest the role of dopamine systems in the reinforcing effects of cocaine in rats (31).

Animal Models of The Deprivation Stage

Withdrawal from chronic drug use is often characterized by reactions that are the opposite of the acute and initial effects of the substance. Many of the physical symptoms that occur during withdrawal from drugs such as alcohol and opioids in animals can be easily quantified, thus providing an important indicator for studying the neurobiological mechanisms of addiction (39). Standardized rating scales have been developed for opiate, nicotine, and alcohol withdrawal. However, measuring the motivational aspects of withdrawal is more relevant for understanding the counter adaptive mechanisms that drive addiction. The measures are discussed below and they are highly sensitive in identifying the motivational aspects of drug withdrawal (35).

Animal models that have examined motivational withdrawal effects include operant mechanisms, conditioned place aversion, intracerebral self-stimulation (ICSS), elevated plus maze, and drug discrimination. Some reflect the general bad feeling of withdrawal, while others reveal more specific components (8).

Threshold Increase in ICSS

Withdrawal from all major drugs after chronic use increases ICSS thresholds, meaning reward sensitivity decreases.

Conditioned Place Avoidance Response (CPA)

The aversive stimulus effects of withdrawal can be measured by conditioned place aversion, a variant of CPP. One method used in opioid addiction is to induce withdrawal by administering low dose naloxone. Although naloxone alone produces place aversion in nondependent rats, the threshold dose required to produce place aversion in dependent rats is significantly reduced. Place aversion has also been observed in induced nicotine withdrawal and acute spontaneous ethanol withdrawal.

Anxiety-Like Responses

Anxiety-like behaviors that increase with drug withdrawal can be assessed with height avoidance (elevated plus maze) or defensive burying tests.

Drug Self-administration in Long-Term dependent Animals

An important feature of the development of addiction is the increase in frequency and quantity of use over time, which is also a DSM-IV diagnostic criteria (18). Extended access models have frequently seen a transition from initial use to higher doses. Recently, animal models of prolonged drug self-access and models of drug self-administration during withdrawal in dependent animals are useful for understanding the transition from drug use to addiction. In rats with induced alcohol dependence, it was observed that ethanol intake was approximately doubled after the withdrawal period and the animals were able to maintain blood alcohol levels of 100-150mg% for 12 hours (8). This phenomenon, called the "withdrawal effect," has been observed in mice, rats, monkeys, and social drinkers.

Overview of Deprivation Phase in Animal Models

The motivational effects of withdrawal in humans (dysphoria, anhedonia elements, loss of motivation, anxiety, and irritability) are also observed in these animal models. Increase in ICSS thresholds has high predictive value, impairment in operant responding indicates at least a general state of discomfort, while drug

discrimination provides a sensitive and powerful method for comparing other drug's withdrawal states. Acamprosate and naltrexone have been shown to be more effective in reducing alcohol intake in addicted rats.

In models of prolonged use, an increase in breaking point (the point at which the subject stops trying when no new reward is received) of the progressive ratio reward for substances such as cocaine, methamphetamine, heroin, and nicotine means that the motivation to seek the substance or the reward of the substance increases.

As more data emerge to explain the neurobiological basis of negative mood in animals and as comparisons with similar negative mood in humans are made, the construct validity of these models will be strengthened. Increased drug consumption with prolonged use has been replicated in many times and has been linked to mechanisms of cross-system tolerance and reward allostasis.

Multiple variables used to understand the motivational effects of withdrawal may provide a framework for identifying overlapping neurobiological bases. Finally, the reinforcing properties of drugs may also change with addiction (8). Evidence from behavioral measures (response impairment, reward threshold change, conditioned place aversion) suggests that addiction alone may lead to an aversive motivational state (40).

Animal Models of The Preoccupation/Craving Stage

The most important feature of addiction is that it follows a chronic and relapsing course. In animals, "relapse" has been studied in three ways:(1) drug-priming induced renewal, (2) cue-based renewal, and (3) stress-induced renewal (41).

Drug-priming Induced renewal

Injecting a small dose of the drug into animals whose drug seeking has been extinguished will cause the drug seeking behavior to dramatically increase again (8).

Cue Based renewal

The auditory, visual, etc. cues associated with the drug alone can rekindle the old "lever" or "button" pressing behavior (42).

Cue induced renewal without extinction(relapse)

In humans, relapse can occur when drug cues are exposed in everyday life without overt "extinction," and in the laboratory, drug seeking increases dramatically in animals when cues are given after "forced remission" (42).

Stress induced renewal

Stress and anxiety are among the most common triggers for relapse in humans, and in animals, stressors such as electric shock, starvation, cold, social defeat, and yohimbine reactivate extinguished drug-seeking behavior (43).

Second Order Reinforcement Schedules

It refers to two-stage complex reinforcement systems in which a neutral stimulus becomes the reinforcer of another neutral stimulus. Second-order reinforcement schedules are a complex system formed by combining two different reinforcement programs.

Animals are trained to associate a repetitive stimulus, initially neutral, with a drug—for example, a tone is played every time a lever is pulled 10 times, followed by 100 sounds and then the drug is administered.

These setups examine how animals can sustain neutral behaviors at extremely high intensity in anticipation of drug availability. This approach allows for modeling drug seeking behaviors absence of the drug (44).

Protracted Abstinence

Even if physical and motivational withdrawal symptoms disappear, an individual who has reached a level of addiction can quickly reverse to their previous level of addiction when they start using the substance again. In animal models, when access to the substance is provided again weeks after the cessation of chronic alcohol or opioid use, tolerance develops much more rapidly and use above previous doses can be observed in a short time (8, 45).

Overview of Animal Models of Addiction

Overall, many of these models have good predictive validity for at least a particular stage of the addiction cycle. The motivational effects of withdrawal are examined by ICSS threshold elevation and anxiety measures. Cue, drug, or stress-induced renewal models are used in the craving phase. Important parallels have been demonstrated between animal findings and human relapsing behavior.

These models provide insight into mechanisms in addiction, from changes in the reward system to negative affect and exaggerated responses to stress.

Conclusion

Animal models are experimental tools designed to investigate and better understand phenomena observed in humans. Due to inherent species differences; these models are not intended to fully replicate complex human mental disorders such as schizophrenia, depression, anxiety or addiction. Instead, their aim is to demonstrate and experiment with key features of diseases leading the development of partial models.

The limitations of animal models of schizophrenia are related to our incomplete understanding of the pathophysiology of the disease. Most of the genes associated with schizophrenia thought to exert their effects primarily through prefrontal cortex. However, many of the susceptibility gene mutation models fail to demonstrate penetrance, possibly because animal prefrontal cortex is not as developed as that of humans. Despite this challanges, pharmacological (dopamine/glutamate) and neurodevelopmental lesion approaches can be applied with behavioral tests that partially reflect positive, negative and cognitive symptoms (locomotor activity, PPI, latent inhibition, social withdrawal and executive function tests).

Addiction models are also partial models and each reflect the stages of intoxication, withdrawal, and craving. They offer high face and predictive validity for respective stages. However, construct validity remains the weakest aspect of such models.

Approaches that focus on reward deprivation in depression (e.g. intracranial self-stimulation, progressive ratio response) or those with strong predictive validity for anxiety (elevated plus maze, conflict tests, etc.) are commonly used. These models have remained at the forefront because of their widespread application in drug development studies.

In modeling depression and anxiety disorders, paradigms focused on the monoamine hypothesis have been extensively utilized, while many other factors involved in the etiology of these disorders (such as inflammation, apoptosis, cytokine-mediated stress pathways, growth factors, genetic and epigenetic factors and nutrition) have not been adequately modeled. Incorporating these factors could be pivotal for improving construct validity in anxiety models. In addition, resilience to neurotic disorders is at least as important as predisposing factors, yet it has received very little attention. Future studies should therefore focus on models of pathophysiology. Shared genetic and epigenetic markers between humans and animals could serve as promising targets for future interventions.

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