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A REVIEW ON ANIMAL MODELS RELATED TO DEPRESSION

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ABSTRACT

The enormous health burden associated with depression is a result of both, the high prevalence of depressive disease and the inadequate efficacy of currently available pharmacological therapies. It is impossible to reproduce depression in animal models because there is a lack of a fundamental grasp of the underlying illness mechanisms in this condition. The current models of depression aim to create in experimental animals measurable correlates of human symptoms. The extent to which the models generate characteristics like a depressive state varies, and models that take stress exposure into account are frequently used. Learned helplessness, the forced swim test and tail suspension test are paradigms that use acute or sub-chronic stress exposure paradigms. Modern models are either based on modifying the environment to which rodents are exposed (during development or adulthood) or on genetic components (e.g., gene deletion or overexpression of candidate genes, targeted lesions of specific brain regions, electrophysiological control of specific neuronal populations, etc.). These modifications can change behavioral and biological results that are connected to various main depressive symptomatic and pathophysiological features. These techniques use brief exposure to unavoidable or uncontrollable stress and can accurately detect an antidepressant drug response. Long-term models, which may more precisely reflect the processes that result in depression, include chronic mild stress models, early-life stress models, and social conflict models.

Keywords: Depression, Antidepressant, Animal models, Validity

INTRODUCTION

Changes in emotion, thought, behaviour, and physical health are symptoms of the persistent mental disease known as depression. A common but serious illness that impairs one's ability to enjoy life and perform even the most elementary everyday tasks. The signs of severe mental illness are not only chronic, but they are also potentially lethal and regularly resurface. Unipolar depression, one of the leading causes of disability-adjusted life years (DALYs), affects 280 million people worldwide, according to the World Health Organization (WHO). When you consider the amount of research done and how frequently the public uses it, depression is one of the most prevalent psychological concepts. But there is misinformation about what depression is, and this misinformation regularly changes how people perceive feelings, symptoms, disorders, and diseases. However, uncertainty exists as to what depression entails, leading to a shift in how we view certain symptoms, syndromes, and diseases. It is also frequently used as a synonym for other alterations, such as "melancholy" **[1]**. In light of the previous, the current study's objective was to investigate the term "depression," beginning with its definition and inspiring additional considerations of the state of the field. The terms "depression" and "deprimere" are derived from Latin. De means "down," and premere means "push," therefore the word deprimere means "press down". In essence, the word appears to refer to a sense of heaviness, of sinking, of being sorrowful, or of being just "down." Dysphoria, the start of a low mood, and anhedonia, the loss of interest in once-enjoyable activities, are the characteristics of major depressive disorder (MDD). These symptoms must last for at least two weeks. One of the major contributors to disability globally is major depressive illness. It is believed to make a number of medical diseases, including diabetes, kidney disease, cancer, and cardiovascular disease are more likely to occur, advance more quickly, and respond less well to treatment **[2]**.

MODELS

Learned Helplessness

Animals exposed to unpredictable unpleasant events, such as an unpleasant unconditioned stimulus (US) that cannot be anticipated, prevented, or avoided, manifests a deficit in their ability that will help them escape from future unpleasant situations. This behaviour is known as learned helplessness (LH), and it is a psychological condition recognized and used to explain the phenomena. The animal exhibits a transitory deficit in establishing an adaptive instrumental contingency, the US

escape reaction, even though the US can now be foreseen (since it is accompanied by a conditioned stimulus (CS) such as a sound or light). The LH test is divided into two stages. Generally, rats are placed in a shock chamber for 40- 60 minutes and subjected to inescapable foot shocks of around 1- 2 mA for a length of 5–15 sec at various intervals, so that the total shock duration is roughly equal to half of the session time **[3][4]**. Rats placed in the shock chambers as the control and the US-preexposed (US-PE) group do not receive any US exposure (US-NPE). To demonstrate the uncontrollable relevance of US impact in the emergence of the LH state, the original LH study comprised both, a group that could avoid the US and a yoked group that could not. 24 hours later, the same type of aversive US plus a novel CS (such as sound or light) are offered to US- PE and US- NPE rats in a conditioning room. This chamber can either be an operant chamber with a lever or a two-way shuttle chamber separated in to two by a barrier. All the animals are given the chance to avoid or flee shock during a later stage when testing for effects of helplessness is conducted. Animals pre-exposed to the inevitable shock under these circumstances exhibit deficits in learning and performance on the test task when compared to animals pre-exposed to the escapable or no-shock conditions, according to a number of studies. Additionally, the fact that both inescapable and escapable partners experience the identical shock pattern raises the possibility that behavioural disturbance is caused by the shock's uncontrollability rather than its actual effects. It has been consistently demonstrated that this phenomena occurs in a wide range of species, including humans, dogs, cats, and fish **[5][6]**.

Forced Swim Test

The forced swim test (FST), devised to evaluate antidepressant (AD) medications and therapies in rats and mice, is still frequently used for this original purpose today, as well as to examine the consequences of exposure to potentially challenging situations by simulating symptoms of depression. In the FST, a rat or mouse is placed in a cylinder with just enough water to keep its hind paws from touching the bottom surface. A typical animal will act quickly, then try to flee until finally adopting an "immobile" stance in which it will only move enough to keep its head above the surface. When clinically useful ADs are administered to mice in the most basic form of the test, immobility time is measured and found to reduce without an increase in overall locomotor activity. The FST is modified for rats to include two test exposures separated by 24 hours, with

medication administered prior to the second exposure. A decrease in immobility time is evidence of an antidepressant's efficacy above water. Prior exposure to the assessment, often done 24 hours before the test, may facilitate the development of immobility **[7]**. The duration of immobility in rats and mice is measured over a brief test period, and conventional antidepressants such as monoamine oxidase inhibitors, tricyclic, and atypical antidepressants all tend to shorten it in a dose-dependent way. It is possible to distinguish between the behaviour following treatment with serotonin-selective antidepressants and the behaviour in response to selective norepinephrine medications in rats by using a modified FST method. Separately quantifying preferred active behaviours, such as swimming or climbing, is one modification. The FST can distinguish between the two because serotonergic antidepressants predominantly have a swimming activity while noradrenergic medicines primarily have a climbing response **[8][9]**. Drugs that increase locomotor activity and consequently decrease immobility can cause the FST to produce false-positive results (eg, amphetamine). Furthermore, FST does not distinguish between the effects of acute and long-term antidepressants equally. The strain differences in activity and medication effects in rats and mice show that the FST is vulnerable to genetic variation **[10]**.

Tail Suspension Test

The TST is said to be more sensitive and shares conceptual similarities with the FST. Animals are positioned 50 cm off the ground, with an adhesive tape applied one centimetre from the tail tip. The animal's immobility will be measured over the course of six minutes. When an animal does not move at all, hangs passively, or is entirely still, it is said to be immobile. The idea of this experiment is that antidepressants typically reduce the frequency and length of immobility, which is caused by short-term stress and the inevitable hanging of animals by their tails **[11][12]**. While having a conceptually similar basis, the TST and FST do not show the similar sensitivity to pharmacological drugs or to strain alterations. This implies that substrates that are not similar may influence response in these tests **[13][14]**. The TST demonstrates that this test is subject to genetic influence by showing that different mice strains respond to basal immobility differently. Due to rats' larger size and weight, the TST is only utilised on mice. Similar restrictions apply to the TST and the FST, such as acute drug reaction and false positive responses to psychostimulants **[15]**.

Chronic Unpredictable Mild Stress

The CUMS model predicts that animals would experience different stressors in unanticipated ways. Homeostasis is disturbed by CUMS, which also results in physiological, neurological, biochemical, and behavioural problems. It was first established on the basis of etiological significance because persistent, fluctuating, unexpected, and unmanageable stress—a known risk factor for depression—causes the disease in animals. Anhedonia, or the inability to feel pleasure, is one of the main effects of CUMS and is frequently observed in rodents, as evidenced by their affinity for sucrose solution. Since its development, the CUMS model has grown to be incredibly popular and is utilised by several laboratories worldwide. As a result, CUMS exhibits strong face and concept validity and resembles stress-induced behavioural alterations that reflect several essential characteristics of major depressive disorder. Antidepressant therapy can also improve CMS-induced depression-like alterations, demonstrating the pharmacologic sensitivity of CMS-induced pathology. For several weeks, rats or mice are subjected to a variety of stressful situations **[16][17]**. Each day, six to eight stressors are utilised for many hours (1 or 2 per day). The use of artificial lighting at night, starvation for extended periods of time, cage tilting, and seclusion or overpopulation are examples of common stresses. The risk of the animals becoming accustomed to any one recurring circumstance is decreased by the sequential and unexpected stress exposure **[18]**. Other behavioural and physiological alterations brought on by exposure to CUS include a decrease in reward-related behaviour, a decrease in self-care, and alterations in sleep patterns that are responsive to antidepressant therapy. These alterations are comparable to the symptoms of depression. These abnormalities support the model's face validity, as do others such as increased hypothalamic-pitutary-adrenal (HPA) axis activation and immune system abnormalities. When compared to the more acute stress models, these alterations show greater face validity as they occur gradually over time with CUS exposure. Construct validity for CUS is based on the development of reduced sucrose preference, which is assumed to reflect anhedonia, a key symptom of depression **[19]**.

Early Life Stress

A recognised risk factor for adult mood and anxiety problems is early childhood trauma. To address concerns about the implicit nature of the maternal separation manipulation, the researchers developed an alternate strategy to decrease maternal care with a limited bedding/nesting paradigm. While others just restrict nesting materials, the most severe

application of the concept is confining dams to cages with wire mesh bases and no bedding or nesting materials **[20]**. As a result, there is a rise in maternal anxiety and fragmented caring, and it is possible to identify the action towards the pups as abusive. **[21]** Some research that used this manipulation showed evidence of increased anxiety and depressive-like behaviour in adulthood, demonstrating the translational validity of the maternal separation model, just as with prior investigations of the paradigm. Several studies using this model have not found increases anxiety and depressive-like behaviour, contrary to those reported with the maternal separation model, raising questions about its validity. It should be noted, nonetheless, that a given mouse strain's unique genetic variations may play a significant role in determining susceptibility to such behaviours. Therefore, it is possible that some animals will be more affected by ELS manipulations than others, and this variability may conceal behavioural differences among groups as a whole **[22]**. Second, consideration should be given to the animal's gender. Given that females are more likely than males to experience mood/anxiety problems, multiple rat investigations have revealed that ELS either has no impact or lowers anxiety- and depression-like behaviours in females **[23]**. It has been hypothesised that maternal behaviour plays an important part in establishing emotional behaviour in offspring by "translating" external stressors into the offspring's appropriate emotional reaction. Many maternal deprivation paradigms separate already weaned rats from their mothers repeatedly in cycles. During the first two weeks after birth, prenatal rats are exposed to everyday sessions of separation lasting between three and six hours. Healthy litters may be separated from the mother, or individual pups may be kept apart from their mother and other pups. When phenotypic features are considered, previously isolated animals can develop to adulthood under normal circumstances. Formerly isolated adult rats have aberrant behaviour, such as elevated fear and anxiety responses, decreased physical activity, decreased social interest, decreased hedonic response, disturbed sleep and food, and endocrine and neurochemical alterations in stress-related systems.

Prenatal Stress - Prenatal stress paradigms have also been used to model the effects of stress. Increased anxiety, higher depression scores in depression models, and abnormal HPA axis activity are all effects of various types of maternal stress, such as exposure to noise or restriction during pregnancy **[24]**.

Social Defeat

The resident-intruder test, also known as social defeat, uses interpersonal conflict among species members to induce both psychological and emotional stress. When a male rodent is brought into the residence of an older, aggressive, dominating male, the conflict is set off. In some cases, the intruder is substituted with a female cohabiting the resident cage, while in other models, intruders are introduced to a resident who had previously been kept apart. In every scenario, the dominant rodent pounces on the invader and knocks it down, forcing it to surrender for the rest of the physical contact. The invader will assume a docile, reclining position when it is unable to flee, producing frequent sounds of distress and exhibiting a frozen behaviour **[25]**. But the feeling of failure is not just a physical stressor. Intruders are frequently put in a protected cage for the duration of the test after a brief physical exposure and attack, allowing for psychogenic stimulation to the resident without causing physical harm. As repeated social defeat results in chronic psychological stress without habituation, such a paradigm is supported by ethological and ecological validity **[26]**. Contrary to other common stressors, particularly moderate stressors, animals readily adjust to habituation after the third or fourth encounter. Social defeat results in a variety of significant physiological and behavioural alterations. The invader experiences an increase in heart rate, higher blood pressure, and increased levels of corticosterone and adrencorticotropin hormone (ACTH) after coming into contact with a resident rat. Intruders already exhibit indicators of stress after coming into contact with aggressive rats or mice, including elevated glucocorticoid activity, tachycardia, and hyperthermia, which take several hours to resolve. Even a single setback can result in significant physiological changes, many of which persist for days after exposure, including alterations in daily body temperature rhythms, growth inhibition, sensitivity to other stressors, and increased anxiousness. Chronic antidepressant therapy is effective in treating social withdrawal and anhedonia brought on by social failure, but not acute treatment **[27]**.

Hedonic Sensitivity

These models have been put forth to simulate particular psychological functions (such as reward) that are impaired in depressed people and are also thought to be a harmful manifestation of schizophrenia. These models instead provide functional assessments of anhedonia, a key component of depression and a harmful symptom of schizophrenia, and are therefore not thought of as models of a

complete disease. "A significant loss of interest or enjoyment in almost all activities for the majority of the day, almost every day" is the definition of anhedonia in humans. A discussion of the intracranial self-administration (ICSS) model, sucrose intake, and location preferences reveals the importance of evaluating the independent variable (i.e., inducing condition) separately from the supply dependent variable, functional measure of the feature of interest. The ICSS model involves short-term electrical self-stimulation of certain brain regions, which is rewarding because it shows that animals will work with it. Response rates for ICSS and psychoactive threshold(s) for ICSS were used as a measure of stimulus reward value **[28]**. Numerous studies have shown that ICSS thresholds are accurate predictors of reward, spanning a wide range from hedonia to anhedonia. The reward value is considered to grow as the threshold decreases, whereas the reward value is considered to drop when the threshold increases. It is thought that ICSS is an important tool for understanding the operation of the brain reward system since it appears to work directly on a number of brain mechanisms that regulate the rewarding effects of natural reinforcers like food and water. In addition, by stimulating the putative reward circuit(s), the system input can avoid this, thereby eliminating confounding effects related to consumer behaviour that could complicate the data interpretation. In addition, because the ICSS threshold estimates are stable for several months, the threshold measurements provided by the ICSS methods are easy to determine and highly reliable **[29]**.

Hyponeophagia paradigms

Reducing food intake in response to new environments, known as "hyponeophagia," has a long history in assessing emotions and anxiety. Models based on hyponeophagia are conflicting trials in which animals are given the choice of accessing and consuming desired foods in a new environment or avoiding a new environment. These models are "ethically appropriate" and therefore do not require complex training procedures, do not confuse painful stimuli, are easy to perform, and are inexpensive **[30]**. Reducing food intake in response to a new environment, known as "hyponeophagia," has a long history in assessing emotions and anxiety. It will be possible to identify and monitor potential changes in consumption-related variables by including home cage controls, which use equivalent measures in the home cage. The use of palatable meals or drinks as test agents prevents insufficient use of foods, which can make interpretation more difficult. The

predictive value of these hyponeophagia models is high. They react to the benzodiazepine and barbiturate anxiolytic effects as well as those of anxiolytic antidepressants. It's crucial to keep in mind that the reaction's time course might also affect how accurate a prediction is **[31] [32]**.

CONCLUSION

The majority of animal models of depression have been shown in this review to correspond to the construct, face, and predictive validity definitions of validity. Furthermore, they imitate depressive behaviours seen in humans and elicit neural alterations reversible by traditional ADs. Despite the fact that these experiments are responsive to the known antidepressant pathways, it's possible that they are not sensitive to alternative processes that could be helpful in the treatment of depression. Models that can precisely mimic key processes happening in depression are vital for the development of novel and improved antidepressant mechanisms. The best models for assisting this will be those that account for stress exposure, time-dependent induction and treatment response, and individual variations in susceptibility.

REFERENCES:

[1] Fekadu N, Shibeshi W and Engidawork E, Major Depressive Disorder: Pathophysiology and Clinical Management, Journal of Depression and Anxiety, 06(01), 2017.

[2] Kanter JW, Busch AM, Weeks CE, *et al*, The nature of clinical depression: Symptoms, syndromes, and behavior analysis, The Behavior Analyst, 31(1), 2008, 1–21.

[3] Overmier JB and Seligman ME, Effects of inescapable shock upon subsequent escape and avoidance responding, Journal of Comparative and Physiological Psychology, 63(1), 1967, 28–33.

[4] Vollmayr B and Henn FA, Learned helplessness in the rat: improvements in validity and reliability. Brain Research Protocols, 8(1), 2001, 1–7.

[5] Pryce CR, Rüedi-Bettschen D, Dettling AC, *et al*., Early-life environmental manipulations in rodents and primates: Potential animal models in depression research, Handbook of Stress and the Brain - Part 2: Stress: Integrative and Clinical Aspects, 2005, 23–50.

[6] Duman CH, Models of Depression, Hormones of the Limbic System, 2010, 1–21.

[7] Porsolt RD, Bertin A and Jalfre M, "Behavioural despair" in rats and mice: Strain differences and the effects of imipramine, European Journal of Pharmacology, 51(3), 1978, 291–294.

[8] Armario A, The forced swim test: Historical, conceptual and methodological considerations and its relationship with individual behavioral traits, Neuroscience & Biobehavioral Reviews, 128, 2021, 74–86.

[9] Detke MJ, Rickels M and Lucki I, Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants, Psychopharmacology, 121(1), 1995, 66–72.

[10] López-Rubalcava C, Strain Differences in the Behavioral Effects of Antidepressant Drugs in the Rat Forced Swimming Test, *Neuropsychopharmacology*, 22(2), 2000, 191–199.

[11] Campos MM, Fernandes ES, Ferreira J, *et al*, Pharmacological and neurochemical evidence for antidepressant-like effects of the herbal product Catuama, Pharmacology Biochemistry and Behavior, 78(4), 2004, 757–764.

[12] Salehpour F, Mahmoudi J, Sadigh-Eteghad S, *et al*., Photobiomodulation for depression in animal models, Photobiomodulation in the Brain, 2019, 189–205.

[13] Bai F, Li X, Clay M, *et al*, Intra- and interstrain differences in models of "behavioral despair", Pharmacology Biochemistry and Behavior ,70(2–3), 2001, 187–192.

[14] Ripoll N, David DJP, Dailly E, *et al*., Antidepressant-like effects in various mice strains in the tail suspension test, Behavioural Brain Research, 143(2), 2003, 193–200.

[15] Lucki I, The forced swimming test as a model for core and component behavioral effects of antidepressant drugs, Behavioural Pharmacology, 8(6), ,1997, 523–532.

[16] Markov DD and Novosadova EV, Chronic Unpredictable Mild

Stress Model of Depression: Possible Sources of Poor Reproducibility and Latent Variables, Biology, 11(11), 2022, 1621.

[17] Strekalova T, Liu Y, Kiselev D, *et al*., Chronic mild stress paradigm as a rat model of depression: facts, artifacts, and future perspectives, Psychopharmacology, 239(3), 2022, 663–693.

[18] Tannenbaum B, Tannenbaum GS, Sudom K, *et al*., Neurochemical and behavioral alterations elicited by a chronic intermittent stressor regimen: implications for allostatic load, Brain Research, 953(1–2), 2002, 82–92.

[19] Willner P, Chronic Mild Stress (CMS) Revisited: Consistency and Behavioural-Neurobiological Concordance in the Effects of CM, Neuropsychobiology, 52(2), 2005, 90–110.

[20] Walker C-D, Bath KG, Joels M, *et al*., Chronic early life stress induced by limited bedding and nesting (LBN) material in rodents: critical considerations of methodology, outcomes and translational potential, Stress 20(5), 2017, 421–448.

[21] Rice CJ, Sandman CA, Lenjavi MR, *et al*., A Novel Mouse Model for Acute and Long-Lasting Consequences of Early Life Stress, Endocrinology 149(10), 2008, 4892–4900.

[22] Murthy S and Gould E, Early Life Stress in Rodents: Animal Models of Illness or Resilience?, Frontiers in Behavioral Neuroscience,2018, 12.

[23] Altemus M, Sarvaiya N and Neill Epperson C, Sex differences in anxiety and depression clinical perspectives, Frontiers in Neuroendocrinology. 35(3), 2014, 320–330.

[24] Morilak DA and Frazer A, Antidepressants and brain monoaminergic systems: a dimensional approach to understanding their behavioural effects in depression and anxiety disorders, The International Journal of Neuropsycho-pharmacology, 7(2), 2004, 193–218.

[25] Blanhard RJ and Caroline Blanchard D, Aggressive

behavior in the rat. Behavioral Biology, 21(2), 1977, 197–224.

[26] Tidey JW and Miczek KA, Acquisition of cocaine self-administration after social stress: role of accumbens dopamine, Psychopharmacology 130(3), 1997, 203–212.

[27] Hollis F and Kabbaj M, Social Defeat as an Animal Model for Depression, ILAR Journal, 55(2), 2014, 221–232.

[28] Markou A and Koob GF, Construct validity of a self-stimulation threshold paradigm: Effects of reward and performance manipulations, Physiology & Behavior , 51(1), 1992, 111–119.

[29] Moreau J-L, Jenck F, Martin JR, *et al*, Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats, European Neuropsycho-pharmacology, 2(1), 1992, 43–49.

[30] Dulawa SC and Hen R, Recent advances in animal models of chronic antidepressant effects: The novelty-induced hypophagia test, Neuroscience & Biobehavioral Reviews, 29(4–5), 2005, 771–783.

[31] Belzung C, El Hage W, Moindrot N, *et al*, Behavioral and neurochemical changes following predatory stress in mice, Neuropharmacology, 41(3), 2001, 400–408.

[32] Dulawa SC, Holick KA, Gundersen B, *et al*, Effects of Chronic Fluoxetine in Animal Models of Anxiety and Depression, Neuropsychopharmacology, 29(7), 2004, 1321–1330.