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A REVIEW ON EXPERIMENTAL ANIMAL MODELS FOR ANXIETY DISORDERS IN RATS

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ABSTRACT

Anxiety has a profound influence on both human and animal behaviour. Both the psychological and biological aspects of anxiety are needed for anxiolytic drug evaluation. Animal models are used as screening methods in the search for compounds with therapeutic potential in the field of anxiety research and as simulations for research on processes that underlie emotional actions. Animal models of anxiety have been optimised mainly for rats, with a mixed performance for mice, an easy-to-use mammal with stronger genetic possibilities than rats. We based on the most commonly used animal models for anxiety in mice in this study. To reflect all types of animal models of anxiety, both conditioned and unconditioned models are highlighted. Strong care for variable parameters, linked to climate, handling or model, is needed in behavioural studies. In order to facilitate more understanding of neurobiological aspects of anxiety, we study the latest experimental anxiety models such as elevated plus maze apparatus, light dark model, open field apparatus, holeborad apparatus.

KEYWORDS: Anxiety model, Elevated zero maze, Plus maze, Elevated T maze, light and dark box model and Mirrored chamber

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INTRODUCTION

Anxiety is a psychological and physiological disorder characterised by components of cognitive, somatic, mental, and actions. These elements combine to produce an uncomfortable feeling that is commonly associated with anxiety, anxiety, fear, or concern. Anxiety disorders may be viewed as "intact" conditions that almost completely disrupt the individual's everyday existence. This induces a state of unexplained anticipatory apprehension and anxiety about the incidence of even ordinary occurrences in existence. Anxiety is an acute fear state and is characterised by motor sympathetic syndromes of hyperactivity, anxiety, and vigilance. An acute stress response characterised by a state of abnormal or extreme arousal or fear is the most common finding [1]. Anxiety states are controlled by both inhibitory and facilitatory mechanisms that either counter or favour anxiety states.

It has been shown that these neurochemical and neuropeptide processes have effects on different areas of the cortical and subcortical brain that are important for mediating symptoms associated with anxiety disorders [2]. More than 90 percent of their genes are shared by mice and humans, and animal models tend to be a valuable instrument in biomedical sciences, as demonstrated by a notable increase in the number of active laboratories operating in the field [3].

In addition, animal models are especially useful in circumstances where, for ethical and other reasons, the effects of stress cannot be examined in humans. However, it is not easy to choose the biological correlates to study, as issues with animal models of human psychological disorders include: I discrepancies between human and non-human nervous systems; (ii) difficulties in identifying common behaviours between species; and (iii) The need for findings to be extrapolated from animals to humans. These issues most likely represent a substantial difference in the aetiology and intensity of anxious behaviours.

Clinical Categories of Anxiety

- ✓ Generalized Anxiety Disorder is a constant state of extreme anxiety that lacks any apparent cause or concentration. Chronic fear is an important characteristic of this form of anxiety [4].
- ✓ Panic disorder is an assault of intense fear that occurs in combination with marked somatic symptoms such as sweating, unexpected repeated panic attacks, tachycardia, chest pains, shaking, chocking, etc. This anxiety syndrome typically has a general component [5].
- ✓ Post- traumatic Stress Disorder elaborates an anxiety triggered by insistent recall of past stressful experiences [6].
- ✓ Social Anxiety Disorder is characterised by a pronounced and intense fear of performance environments where they believe like they may be the object of attention and do something humiliating or embarrassing. It may be very unique to the situation that triggers this fear, such as public speaking.
- ✓ Phobia is a strong fear of specific things or situations e.g. snakes, open spaces, flying and social interaction.

Neuromodulators Role in Anxiety Disorder

Acetylcholine

In response to anxiogenic and stressful stimuli, cholinergic input to the hippocampus is increased, wherein muscarinic M1 receptors mediate the activation of anxiety states through noradrenergic pathways. On the other hand, nicotine facilitates GABAergic neurons and induces anxiolysis and anxiolysis is also being observed after by increasing acetylcholine levels on administration of acetylcholinesterase inhibitor physostigmine in dorsal or the ventral hippocampus [7].

Norepinephrine (NE)

In the locus ceruleus, the majority of noradrenergic neurons are located. Noradrenergic signalling alteration is associated with anxiety disorders. Sustained activation of the locus ceruleus results in the presence of signs of anxiety. Nor-epinephrine stress-induced release promotes a variety of anxiety-like behavioural reactions, including stress-induced reduction of open-arm exploration on elevated plus-maze, stress-induced reduction of behavioural social interaction [8]. Deficient mice have elevated circulating catecholamines and raised heart rate and blood pressure from the Norepinephrine transporter. Adrenergic beta receptor antagonists have also been clinically used for the treatment of performance anxiety [9].

Gamma-aminobutyric acid (GABA)

GABA is the most concentrated inhibitory neurotransmitter in the central nervous system. In neural tissue, the presence of GABA appears to hyperpolarize neurons. This hyperpolarization occurs when the neurotransmitter of GABA binds to neurons with $GABA_a$ receptors. Chloride ions that are negatively charged are allowed to flow down the chemical gradient and into the cell body of the neuron. The neuron is hindered by this electrochemical negativity and the probability of its firing of further electrical impulses decreases. As GABA and GABA activity levels increase, neuronal firing and activity decrease [10]. Physiologically, GABA is a muscle relaxant and sedative. In anxiety disorders, preclinical and clinical evidence exists for dysregulation of the central GABA-ergic sound. Via Gama Amino butyric acid Transporter-1 transporter blockade, a selective GABA reuptake inhibitor exerts anxiolytic effect by tiagabine, thus facilitating GABA neurotransmission [11]. Herbal anxiolytics such as valerian roots contain large quantities of GABA and possess GABAergic operations.

Serotonin (5HT)

In anxiety, serotonergic neurons are involved in altering appetite, energy, sleep, mood, and cognitive function. The role in anxiety is confirmed by its modulating effect on the locus ceruleus and its amygdal projections; the

anatomical structure is almost conclusively involved in anxiety. Serotonergic pathways are triggered by fear and stress [12].

Cannabinoids

In the hippocampus and cortex, they inhibit the flow of glutamate, norepinephrine and dopamine and interfere with GABAergic transmission in the amygdala, hippocampus and frontal cortex. Both anxiolytic and anxiogenic profiles have been observed because of the dynamic pattern of effect of cannabinoids on the release of neurotransmitters [13].

Cholecystokinin (CCK)

CCK is one of the brain neuropeptides with the greatest abundance. In anatomical locations such as periaqueductal grey (PAG) that mediate anxiety, CCK-immunoreactive fibres and CCK (2) receptors are rich. Neuronal CCK (2) receptor expressions result in anxiety-like activities that are attenuated by diazepam [14].

Melatonin

Sleep and rhythm are dominated by melatonin, which is usually disrupted by anxiety. Melatonins create anxiolysis, which is inhibited by the GABAA receptor antagonist Flumazenil[15].

Glutamatergic Transmission

The levels of glutamate are significantly increased when sensitivity to stimuli and stress occurs [16]. Endogenous excitatory amino acid neurotransmission antagonisms in the neurons of the brain cause behavioural suppression of anxiety. In the elevated plus maze, glutamate antagonists show an anxiolytic-like profile [17].

Various neurochemicals that are involved in anxiety pathology. Pharmacological research using receptor antagonists and receptor knock-out approaches demonstrate that anxiety disorders are the product of fundamental shifts in a number of neurotransmitter system changes.

Experimental Animal Models for Anxiety

In preclinical research on the neurobiology of psychiatric disorders, animal models form the backbone and are used both as screening methods in the search for novel therapeutic agents and as simulations for underlying mechanism studies. Two major sub-classes can be divided into animal behavioural models of anxiety: 1) conditioned models 2) Unconditioned models. The conditioned model incorporates the reactions of the animal to unpleasant and sometimes painful experiences (e.g. electrical foot shock exposure). The unconditioned models include the involuntary or normal responses of the animal (e.g. flight, avoidance and freezing) to stress stimuli that do not directly include pain or discomfort (e.g. exposure to a new , highly illuminated test chamber or a predator).

Table 1: Type of Anxiety Models

Conditioned Models	Unconditioned Models
Four plate method	Open field model
Fear-potentiated startle	Elevated plus maze
Vogel water-lick conflict test	Elevated zero maze
	Elevated T maze
	The light-dark box
	Hole dipping curiosity test
	Mirrored chamber

Conditioned Models

Four Plate Method

The four-plate test (FPT) proposed by Boissier *et al.* is based on the elimination of the mouse 's basic innate continuing actions, i.e. the exploration of new environments. The apparatus consists of a floor consisting of four rectangular metal plates which are similar. The availability of mild electric foot shock dependent on quadrant crossings suppresses this exploration behaviour. The experimenter electrifies the entire floor each time the mouse crosses from one plate to another, evoking a simple flight-reaction of the animal. Benzodiazepines (BDZs) increase the number of penalised animal-accepted crossings. It is important to check that this medication has no analgesic effects until any conclusion can be drawn about a drug tried in this test. This is verified utilizing a hot-plate apparatus, employing morphine as the control compound [18].

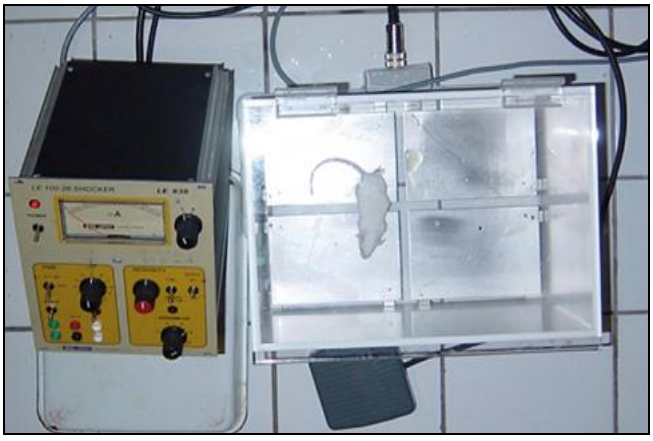

Figure 1: Four Plate Test

In addition, FPT facilitates the analysis of the underlying mechanism of anxiety, such as inter-regulation between receptors of the 5-HT2 subtype and noradrenergic alpha2 receptors. Our laboratory has confirmed that a single previous undrugged FPT exposure decreases punished re-test responses at intervals between 24 h and 42 days. Furthermore, prior experience attenuates the anxiolytic response to the Benzodiazepines diazepam and lorazepam, similar to results observed in the Elevated plus maze and Light and Dark Model.

Fear-Potentiated Startle

This Pavlovian fear conditioning technique, originally developed by Brown *et al*., involves two separate steps. Next, the animals are conditioned to equate an aversive stimulus, such as an electric foot-shock, with a neutral stimulus, usually a flash. Animals are met with an intense sound during practising. The surprising reaction to this unconditioned stimulus is potentiated by the presentation of the previously conditioned light stimulus simultaneously.

Even 1 month after preparation, this potentiation can be observed. A dose-dependent reduction of the startle mamplitude is induced by Anxiolytics with no improvement in the startle baseline level (observed in the absence of conditioned stimulus). A reduction in the baseline will expose a non-specific disability of the locomotive [19]. Main results of this model have been published by Davis et al. Overall, Benzodiazepines, as well as buspirone-like drugs, decrease fear-potentiated startle, often without any change in the baseline response [20].

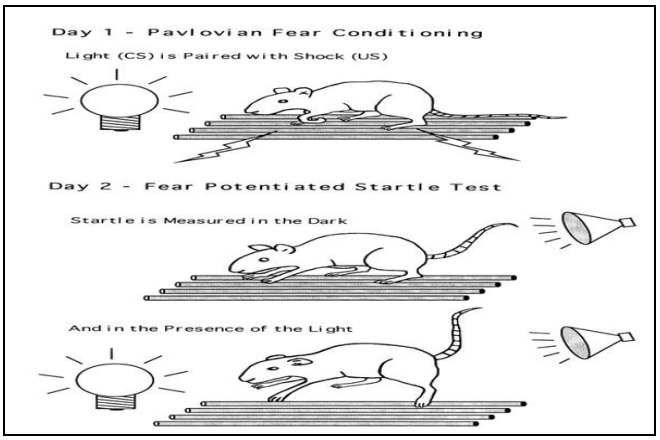

Figure 2: Fear Potentiated Test

Vogel Water-Lick Conflict Test

This test is a well-known procedure used in rats, developed by Vogel *et al.* Only a few studies have attempted to apply the test to other animals, but recently this test has been documented to successfully detect diazepam-like anxiolytic activity and to be ideal as a screening tool for drugs with obvious anti-anxiety behaviour. Thirsty animals receive water rewards through a waterspout in this exercise, but at the cost of having a mild electric shock applied to the tongue [21].

Licking in controls is suppressed, anxiolytics release this suppressed behaviour, while non-specific effects are assessed on non-punished water drinking. Diazepam and pentobarbital produced a significant anti-conflict effect, which means that these drugs increased the number of electric shocks mice received during the test session.

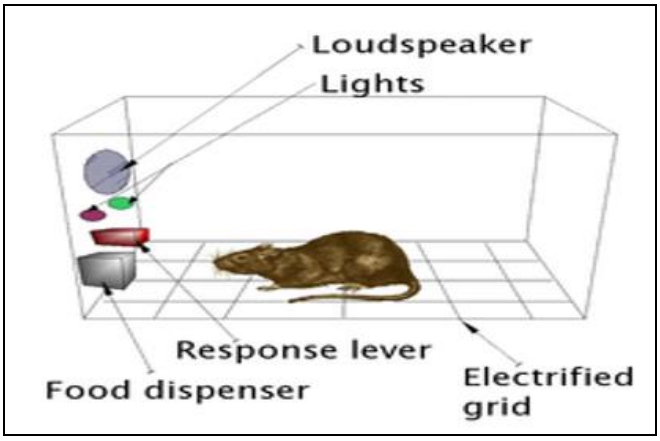

Figure 3: Vogel Water-Lick Conflict Test

Unconditioned Models

Open Field

Originally developed by Hall on rats, this test consists of placing an animal with surrounding walls in an unknown area in order to observe a variety of patterns of behaviour, including the propensity to remain on the periphery of the field without entering the centre (called thigmotaxis and sometimes interpreted as nervous behaviour), defecation and urination levels. The open field floor is mostly split into squares at present.

Animals are tested individually; always being placed in the same position. Anxiety behaviour in the open field is triggered by two factors: individual testing and agoraphobia. Higher levels of anxiety should mainly lead to decreases in the ratio ‘number of squares visited in centre/number of squares visited on periphery [22].

Figure 4: Open Field Test

Elevated Plus Maze

In current practise, elevated plus maze (EPM) is the most utilised animal model of anxiety. Handley and Mithani (1984) first suggested it, and Pellow and File (1986) further validated it. The apparatus is elevated above the level of the floor and consists of two enclosed arms, contrasted by two open arms perpendicularly. The test is based on the natural propensity of rodents to explore novel environments and their inherent avoidance (represented by open arms) of vulnerable, bright and elevated areas.

Open arms confinement causes physiological symptoms of stress (increased defecation and levels of corticosterone), whereas exposure to traditional anxiolytic medications, such as benzodiazepines, improves arms exploration. Several variables, such as living conditions, lighting levels, circadian cycle variability, previous handling or stress exposure, and familiarity with the maze, influence the basal behaviour of the animals in the EPM.

Figure 5: Elevated Plus Maze

Individual accommodation, for example, increases anxiety in rats but decreases it in mice, possibly due to distinct patterns of social organisation between the groups, whereas previous exposure to stress (foot shock, social defeat, exposure to predators) significantly increases anxiety. In addition, re-exposure to the EPM results in marked decreases in the exploratory activity of the open arm and may completely eradicate the anxiolytic effect of benzodiazepines. In addition, the presence of the experimenter in the same room can also interfere with the results. This caveat, however, has been overcome by videotaping the experimental session for later behavioral analysis (with or without the help of specialized software) [23].

Elevated Zero Maze

The elevated zero maze (EZM) is a modification of the Elevated Plus Maze (EPZ) that incorporates both traditional and novel ethological measures for the analysis of drug effects while eliminating the ambiguous interpretation of animal location in the center area of the EPM. The EZM is a circular runway elevated from the floor that alternates open, brightly lit areas with enclosed, dark paths.

Figure 6: Elevated Zero Maze

It is proposed that the uninterrupted nature of the open versus enclosed segments of the circular arena alleviates the problems concerning the center zone of the EPM. Similar to the behavioral measures scored in the EPM, the percent of time spent and the percentage of entries in the open areas of the EZM during the 5-min session are related to anxiety index. In this model, diazepam and chlordiazepoxide significantly increase the percentage of time spent in the open quadrants, as well as other ethological measures, such as frequency of head dips and reduced frequency of stretched attend postures in the enclosed towards the open quadrants [24].

To minimize environmental variables introduced by the presence of the investigator that may impact anxiety-like behaviors, videotaping of the session is also recommended.

Elevated T Maze

The elevated T maze (ETM) was originally proposed by Graeff *et al*. It is based on the EPM and consists of three arms: one enclosed by a lateral wall standing perpendicular to two opposite open arms of equal dimension. The whole apparatus is elevated from the floor. This model allows measurement of two different behaviors in the same animal: the conditioned response represented by inhibitory avoidance of the open arms and the unconditioned response represented by escape behavior when the animal is placed in the extremity of these arms. These responses have been related to generalized anxiety and panic disorders, respectively. The ETM was developed in response to the inconsistencies found in other animal models of anxiety, particularly the EPM, regarding drugs that interfere directly with serotonergic neurotransmission [25].

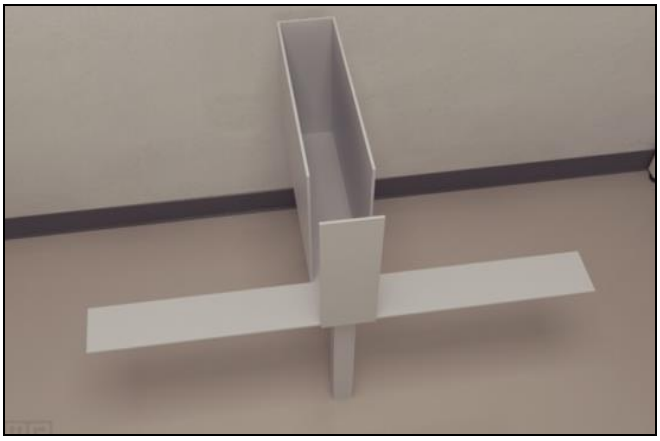

Figure 7: Elevated T Maze

The Light-Dark Box

The light-dark exploration test was developed before the EPM test by Crawley & Goodwin in the early 1980s. Similar to the EPM, this animal model is based on the innate aversion of rodents to places with bright light. Animals are permitted to freely explore a novel environment consisting of two separate compartments during a 5-min session: protected (dark) and unprotected (lit). This model creates an intrinsic conflict in rodents between their exploratory drive and their avoidance of the illuminated compartment. Treatment with anxiolytic medications such as benzodiazepines raises the amount of time spent in the illuminated compartment and the number of changes between the two regions [26, 27]. In this test, as in others that measure exploratory activity, particular attention should be given to drug- or genetic-induced changes in basal locomotor activity or novelty-seeking behavior (e.g., amphetamine treatment), since they could produce false positive results.

Figure 8: Light and Dark Box

Hole Dipping Curiosity Test

The hole dipping induced curiosity in mice, test is carried out for 5 min as animals, peeps through hole cuts a photocell and count is noted down. The placing of albino mice, 30 min after injection with saline or diazepam or test drug, singly on a wooden board with 16 evenly spaced hole and counting the number of times they dipped their heads into holes during 5 min trails is used for evaluations. It is usually observed that there is either significant decrease or increase in head dip responses in mice based on the nature of the test drug [28].

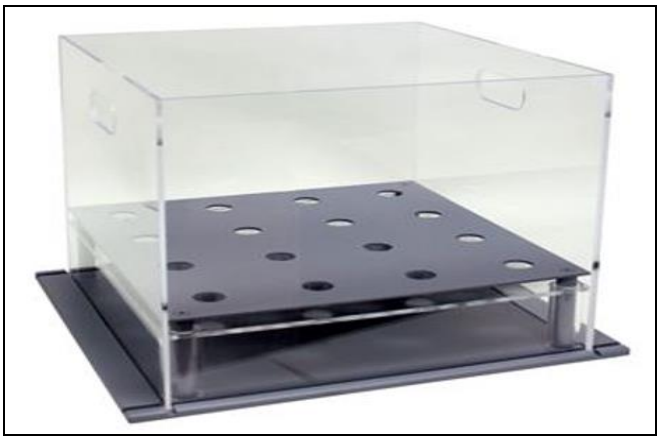

Figure 9: Hole Dipping Test

Mirrored Chamber

Many animal species exhibit approach avoidance responses upon placement of a mirror within their environment. Toubas (1990) developed a mirrored chamber apparatus for

which rat show an extended latency to enter. Novel stimulation evokes both exploration and anxiety, and it's generating an approach-avoidance conflict behavior. The extended latency to enter the chamber of mirrors is used as a parameter for the anxiety analogy, and anxiolytic benzodiazepines such as diazepam and triazolam significantly reduce this latency in a dose-dependent manner [29]. The mirror chamber apparatus essentially consists of a mirrored cube open on side which is placed into a square plexiglass box. The mirrored cube (30 x 30 x 30cm) is constructed of 5 pieces of mirrored glass with one mirrored side and opposite side painted dark brown. The cubical mirrored chamber had its 5 interior surface made of mirrored glass. The container box (40 x 40 x 35.5 cm) has a white floor and opaque black walls. Placement of the mirrored cube into the center of the container forms a 5 cm corridor completely surrounding the mirrored chamber. A sixth mirror is placed on the container wall positioned so that it faces the single open side of the mirrored chamber.

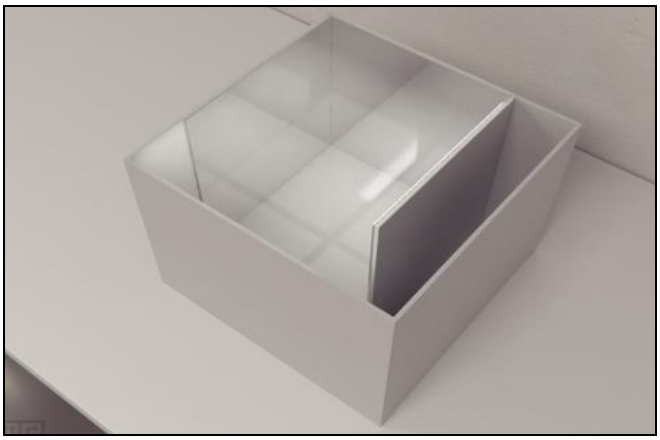

Figure 10: Mirror Chamber Test

Except for this one mirrored portion on the container wall, all portions of the container walls are black. Rats are exposed to the chamber of mirrors and evaluated only once to avoid habituation problems. The focus of this method is to evaluate the latency to enter the chamber of mirrors from the surrounding corridor [30].

CONCLUSION

The number of animal models of stress and anxiety currently available is far greater than when these models were first used for study 50 years ago. This implies it is not always a simple job to select the most suitable model for a particular experiment. Ideally, the theory being tested, the nature of the experiment, the investigator's experience, and knowledge of the model 's weaknesses should be the basis of this decision. Procedures that can monitor false-positive or false negative outcomes and bias caused by local laboratory conditions should be given special attention. The latest analysis has covered some of these aspects. Despite their limitations, animal models are invaluable instruments for studying the neurobiology of anxiety and stress-related disorders.

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CONFLICT OF INTEREST

None

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