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Review

Wistar Rat Model Of Alzheimer's Disease: Behavioral Assessment and Therapeutic Screening

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Abstract

This review highlights their crucial role in screening studies across various fields, including pharmacology, toxicology, neurology, and metabolic research. The ability of Wistar rats to exhibit reproducible biological responses makes them ideal for evaluating the safety, efficacy, and biological effects of new therapeutic agents and chemicals before human trials. Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss. Effective drug development necessitates reliable animal models that replicate human AD pathology. In this study, we utilized a rat model induced by the administration of amyloid-beta ($A\beta_{142}$) peptides into the hippocampus to mimic early-stage AD. Behavioral assessments, including the Morris Water Maze (MWM), Y-maze, and passive avoidance tests, demonstrated significant cognitive impairments 8 weeks post-injection, reflecting typical AD symptoms. The reproducibility and consistency of cognitive impairments observed in this model make it an invaluable tool for screening potential therapeutic agents. By evaluating the efficacy of novel compounds in ameliorating cognitive deficits in this model, researchers can identify promising candidates for further development. Additionally, this model facilitates the investigation of underlying mechanisms of AD pathology, including amyloid deposition, tau phosphorylation, and neuro inflammation.

Keywords: Wister rat, screening model, Alzheimer's disease, Research purpose

INTRODUCTION

Due to their well-documented genetic, physiological, and behavioural traits, Wistar rats (Rattus norvegicus), a strain of laboratory rats that is frequently used, are crucial models in the field of biomedical research.. Among the animals that are utilised in laboratory research, Wistar rats have emerged as one of the most frequently used. Infections caused by parasites and diseases transmitted from animals to humans are most likely to affect rats. In addition, there are ethical criteria, such as the 3Rs, which stand for replacement, reduction, and

refinement.[1] It was initially developed in 1906 at the Wistar Institute of Anatomy and Biology at the University of Pennsylvania, where a colony of albino rats was established. This was the starting point for its development. First and foremost, the objective was to develop a genetically homogenous breed that would be suitable for controlled laboratory trials. [2][3] The Wistar Institute in Philadelphia was the first institution to consciously raise rats into "standardised" laboratory animals. This was done with the objective of satisfying the requirements of scientific study and fostering the expansion of the developing scientific community (Clause, 1993). [4][5]They are noted for their placid demeanour, the simplicity with which they may be bred, and their well-established reaction to a variety of experimental protocols, all of which make them a perfect subject for scientific investigations. Because the strain was selected with the intention of achieving certain characteristics, such as genetic uniformity and a calm temperament, it is suited for a wide variety of research projects. [6][7] 1912 was the year when the Wistar rat began to garner attention, particularly in the fields of genetics and medical research. Because of its genetic homogeneity, it was an excellent model for conducting drug tests, neurological research, and toxicological research. Over the course of its history, the Wistar rat has been instrumental in the development of several medical advancements, including the creation of vaccines and the investigation of cancer. The genetic stability of Wistar rats and their regular responses to treatments make them an invaluable resource in laboratories all over the world (Heston, 1952; Chien & Wang, 2007; Wistar Institute, 2006).[8][9] In addition, Wistar rats continue to play an essential role in preclinical research and regulatory testing processes. Before beginning any research that involves Wistar rats, researchers are obliged to submit a thorough research proposal to the Institutional Animal Ethics Committee (IAEC) or an analogous body.[10][11] This is a requirement that must be met before any research can begin. Detailed information regarding the research aims, experimental technique, and the anticipated use of animals should be included in the proposal. To add insult to injury, veterinarian care is an indispensable component in the process of preserving the health of animals and guaranteeing the accuracy of experimental findings.[11][12][13][14]

Fig 1: Housing Management of Wister Rat

Selection of animal

The breeding colony's normal health monitoring program included screening randomly selected animals for haematology and biochemistry parameters. This activity was carried out as part of the usual health monitoring program. [15][16]The breeding colony animals were picked from either sexes at ages ranging from six to eight weeks, ten to fourteen weeks, and more than six months. The information was gathered from 660 animals, with 110 animals belonging to each gender and three age groups being included in the sample.[17]

Purpose of proper handling

Wistar rats are known for their calm temperament, ease of breeding, and well-established response to various experimental protocols, making them ideal subject for scientific investigations. [18[19] The strain was selectively bred for traits like genetic consistency and calm temperament, making it suitable for a wide range of studies. The successful breeding and management of Wistar rats involve attention to various factors such as optimal mating age, appropriate mating systems, proper care during pregnancy, and effective management of offspring.[20][21] However, breeding Wistar rats requires careful management to minimize genetic drift, ensure high reproductive success and prevent health issues that may arise from improper care or inbreeding. Controlling unwanted mating in Wistar rats during research play a crucial role to maintain the integrity of experimental results,

prevent inbreeding, and ensure proper animal welfare.[22][23] Unwanted mating can lead to complications such as genetic contamination, variability in experimental outcomes, or unintended pregnancies, which can disrupt the research process. Prior to the research, male and female rats should be separated in an ideal ratio to resolve the issue of unwanted mating.[24][25]

However, for most conventional laboratory studies, Wistar rats are typically used when they are about 6 to 8 weeks old, with their average weight ranging between 150 and 200 grams (as per National Institutes of Health). The successful breeding and management of Wistar rats involve attention to various factors such as optimal mating age, appropriate mating systems, proper care during pregnancy, and effective management of offspring.[26][27] Animals were housed in controlled room temperature of 23 ± 2 °C and humidity conditions of 30–70%, with room ventilation set at 10–15 air changes per hour in IVC (ventilation rate set at 40–50 air changes per hour) with a 12-h light/ dark cycle. The animals had access to a standard chow diet (2018 Teklad global 18% protein rodent diets, inotiv) and water ad libitum unless otherwise specified. All the health monitoring procedures complied with CCSEA guidelines and were approved by Institutional Animal Ethics Committee (IAEC). The 6–8 weeks, 10–14 weeks and > 6 months old rats were used in the experiments.[28][29][30]

Screening of Rat in Alzheimer's disease

Alois Alzheimer, a German physician and neuropathologist, delivered a presentation in which he recognised an illness of the cerebral cortex [31] that would eventually be named after him: Alzheimer's disease (AD). This event took place one hundred years ago. Senile plaques and neurofibrillary tangles (NFTs) are both detected in the brains of people who have this disorder [32]. Additionally, the cerebral cortex of these people is thinner than it would be in a normal environment. In the early 1980s, the biochemical characterisation of senile plaques in people with Down syndrome and Alzheimer's disease led to the identification of amyloid-β (Aβ) peptide as a significant component. Following this, it was established that the Aβ protein is a product of the Aβ protein precursor, also known as APP. Based on the fact that hereditary mutations in the APP gene inevitably produce Alzheimer's disease in cases with the early onset familial type of the disease [33–35], it is evident that the role of Aβ/APP in the pathogenesis of Alzheimer's disease is of fundamental significance. Due to the connection between amyloid precursor protein (APP) and amyloid beta (Aβ), the research community exhibited a rapid and enthusiastic response to Aβ, thereby laying the groundwork for the amyloid cascade hypothesis [4,000]. According to the amyloid cascade hypothesis, mutations in amyloid precursor protein (APP) or other genes result in an increase in amyloid beta (Aβ), which in turn leads to the development of disease. A more recent version of the idea [34] suggests that smaller oligomeric forms of Aβ are the key to understanding the disease, in contrast to the original hypothesis [35- 36], which proposed that Aβ fibrils were the primary mediator of the disease. When it comes to both instances, it is believed that Aβ plays a significant role in mediating the neuronal and synaptic toxicity that ultimately results in the decline of cognitive abilities [37]. In a similar vein, a steady stream of studies started to shed light on the function of neurofibrillary tangles (NFTs) and its primary protein component, phosphorylated tau, in the brain, as well as the ways in which these pathological structures are connected to the symptoms of Alzheimer's disease [38]. The majority of researchers in the area are confident that A and NFTs play key roles in the start and progression of Alzheimer's disease (AD). This is despite the fact that the pathological importance of A and NFTs in disease, as well as their interaction, is currently actively being discussed [39,40]. In addition to the aforementioned, there are additional theories of AD that are being actively investigated, which are not related to NFTs or Aβ deposits (for a summary, see [41–45]). In spite of this, the development of transgenic mouse models of Alzheimer's disease (AD) over the past decade has primarily concentrated on the pathological markers, which include neurofibrillary tangles (NFTs) and senile plaques. These transgenic models have become promising tools for determining the mechanistic significance of tau phosphorylation and Aβ deposits, as well as their relationship with each other and other pathological changes. It is essential to keep in mind that the validity of a mouse model of disease is closely connected to the animal's capacity to imitate the symptoms of the disease, which in the instance of Alzheimer's disease is cognitive loss. This may appear to be an apparent fact, but it is a fact nonetheless. The purpose of this review is to examine the cognitive function of transgenic mouse models, with a particular emphasis on Aβ and tau models. Subsequently, the validity of these models for the study of Alzheimer's disease (AD) and the mechanistic problems that have arisen as a result of their behavioural phenotype will be discussed through this review [46,47]. Alzheimer's disease patients exhibit a steady deterioration in cognition, which is primarily caused by the loss of neurones and synapses in the hippocampus formation and surrounding locations [48]. This is the most prominent and noticeable indication of Alzheimer's disease. In light of this, the capability of a true Alzheimer's disease (AD) transgenic model to precisely reflect the behavioural changes that are observed in human Alzheimer's disease patients is a "must have" characteristic of the model. It is essential to have a comprehensive understanding of the behavioural tasks that are most frequently used to test cognitive changes in mice, as well as the specifics of what each cognitive test is truly measuring, in order to appropriately interpret the behavioural results obtained from transgenic mouse models of Alzheimer's disease (AD). When studying the cognitive processes of animals, behavioural tasks are often classified as either associative or operant learning tasks on the basis of their behaviour. In order to condition a certain response in the

animal, associative learning tasks make use of signals that are present in the environment.[49][50] Tasks that include operant learning need the animal to respond in a particular way to a particular stimulus in order for the animal to be able to receive a result. A further division of cognitive tasks into groups is made according to the type of memory that is being evaluated. The following are some of the tasks that are undertaken the most frequently in order to ascertain cognitive changes in mouse models, whether they are transgenic or not.[51]

Spatial Memory Tasks

The Morris Water Maze

In order to investigate age-related or Alzheimer's disease-like deficiencies, the Morris water maze (MWM) is an especially sensitive task. This is due to the fact that it is extremely selective for hippocampus function, which is one of the first and most affected brain regions in Alzheimer's disease [52]. As a consequence of this, the MWM test is one of the numerous behavioural tasks that are utilised to ascertain whether or not there are deficiencies in hippocampus spatial memory [53]. The test involves placing the rat in a circular tank that is filled with hazy water. The purpose of the test is to encourage the animal to swim to a hidden platform that is situated directly below the surface of the water in order to escape the water. Through the use of spatial clues, such as posters or taped objects strategically placed on the walls outside of the water maze, the rodent is able to learn how to locate the concealed platform over the course of several days in the controlled environment of the testing room. [54][55]Measures of this test that are commonly used include the distance swum, the amount of time it took to reach the platform, and the speed at which the swimmer is swimming. By employing a probe trial and a reversal trial, it is possible to test whether or not the animal is able to recover and remember knowledge that it has learnt, as well as whether or not it is flexible enough to purge and relearn new tactics.[56][57] While the animals are participating in the probe trial, the platform is removed, and they are permitted to swim in the pool. The reversal trial is the same as the training trials; however, in this instance, the platform is moved to the opposite side of the pool. This is done in order to evaluate the animal's cognitive flexibility, which is essential for the animal to relearn a new location. It is also possible to utilise a cued variant of this task, which involves making the platform visible, in order to evaluate nonspatial strategies in addition to visual acuity [58]. Additionally, there is the radial arm water maze (RAWM) or the plus-shaped water maze, which are both variations [59][60]

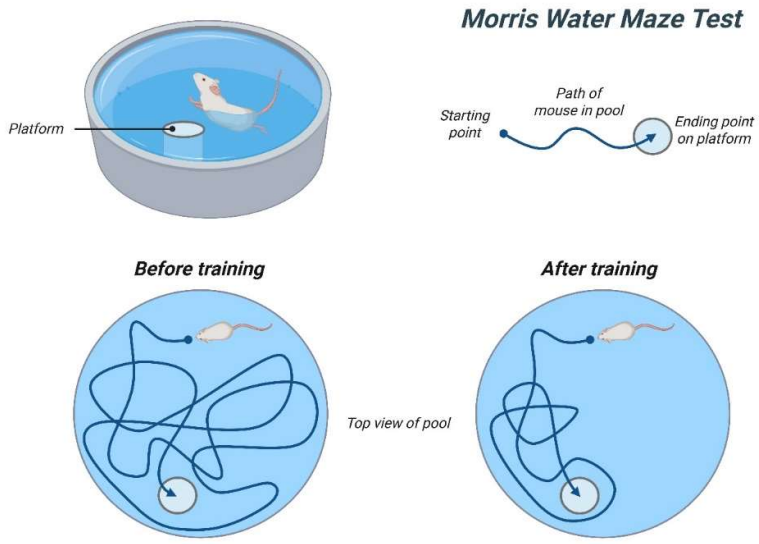

Fig 2: Morris water maze test

The fact that the motivating stimulus, which is avoiding the water, does not involve the loss of food or water, which is a common requirement for other spatial memory tasks, is one of the favourable aspects of this test.[61][62] On the other hand, it does have certain limitations, one of which is that it is not possible to evaluate all of the different aspects of memory at the same time. This includes both the reference and working memories. Time spent in the region that formerly included the platform, time spent crossing over the platform area, and the amount of time it takes to arrive at the location of the platform are all measured[63][64]

Radial Arm Maze

The radial arm maze (RAM) that has been widely utilised to study spatial memory performance in rodents is an example of a task that can enable simultaneous testing of memory components and has also been used extensively in this type of research. It is necessary for the mouse to enter this maze in order to acquire a reward of food or water that is positioned in some of the arms. [65][66] The maze is composed of eight to seventeen arms that are uniformly spaced and radiate outward from a central platform. During this activity, the animals direct themselves around the room by using spatial cues. [68]The objective is to enter each arm just once in order to obtain the greatest possible quantity of food or water rewards in the shortest amount of time and with the least amount of effort. This labyrinth demands the use of working memory to remember information that is significant for a short period of time (within trial information), as well as the use of reference memory to remember the basic principles of the task over the course of several days. To be more specific, the animal must be able to remember which arms were baited as well as which arms it has already entered (working memory), and it must also be able to avoid non-baited arms across trials (reference memory). All of this is accomplished via the animal's ability to successfully encode spatial information. However, despite the fact that this task allows for the study of both reference and working memory, it does have some significant limitations. These limitations include the imposition of food or water restriction during this task, as well as the existence of odour confounds [69,70].

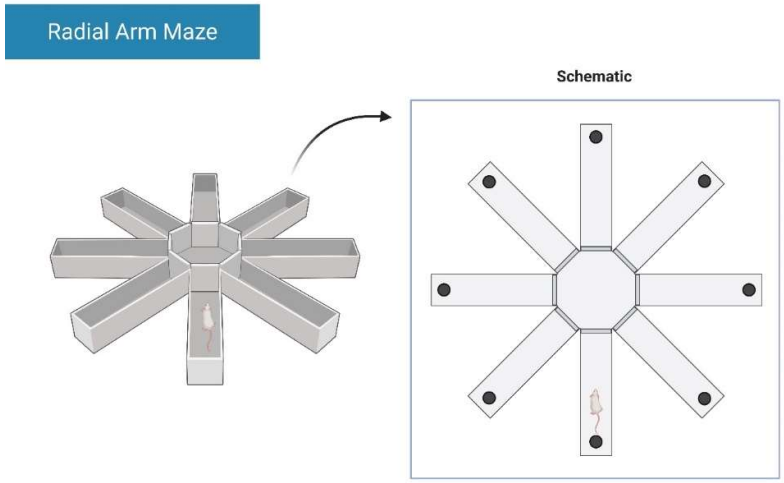

Fig 3: Radial arm maze

Radial Arm Water Maze

By combining the advantageous features of the MWM and RAM, a relatively new spatial memory task known as the RAWM has been developed with the intention of removing the constraints that were present in the tasks that were previously described. When opposed to the traditional MWM, which just consists of an open swim field, the RAWM fig.4 requires the player to identify a platform that is submerged in water and is situated in one of many arms [71-72] within the water bath. This is the primary distinction between the two types of swimming machines. The animal is forced to use spatial cues and working memory (keeping track of the arms it has already visited) in order to remember where the platform is located. This makes the task a little bit more difficult, but it also strengthens its ability to remember. In order to investigate differences in spatial memory following pharmaceutical therapy [73], as well as differences between species [74], gender [75], and, most crucially, models of Alzheimer's disease [24,29], researchers have utilised a variety of different variations of this task. These variations involve varying the number of platforms and the organisation of platform locations.

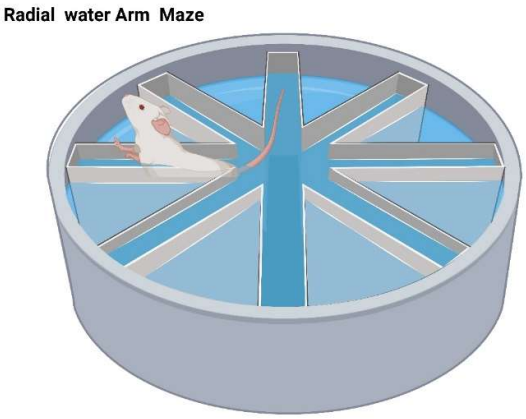

Fig 4: Radial Arm water Maze

Contextual Memory

Fear Conditioning

Rodents have an intrinsic response to fear that is characterised by a complete lack of movement, which is referred to as the freezing response. The animal is placed in a box that has a grid that delivers a mildly unpleasant stimulus for a period of two minutes as part of a paradigm known as fear conditioning. [76][77] A tone (often 80 decibels) is provided to the animal in the box as a conditioned stimulus. This tone is then paired with a minor shock (an unconditioned stimulus) at the conclusion of the experiment. The effect of this combination is that the animal freezes in reaction to the tone used in the experiment. In certain circumstances, repeated exposures may be required, depending on the strain that was applied or the amount of time that passed between the tone and the shock.[78][79] Trace fear conditioning is a method that is utilised by certain researchers in order to evaluate prefrontal cortex activity. This method involves increasing the amount of time that passes between the tone and the shock. In this step, the animal is removed from the box and then brought back twenty-four hours later in order to assess its learnt aversion to an environment that is associated with a moderate unpleasant stimuli (context-dependent fear). This is accomplished by observing the animal's behaviour of freezing in the absence of a tone or aversive stimulus. Cue-dependent fear can be quantified by placing the animal in a new box that is different in colour, shape, and other aspects, and then presenting it with the tone as it explores the new habitat. The freezing behaviour that is linked with the tone is then measured.

When it comes to evaluating hippocampal-dependent associative learning, fear conditioning is a test that is frequently utilised. It is believed that this test is sensitive to learning that is related with emotions, and as a result, it is an effective measurement of communication between the amygdala and the hippocampi. The amygdala is principally responsible for the functioning of fear and anxiety, and many of the transgenic animal models of Alzheimer's disease have deficits in these areas. The hippocampus function that is utilised in fear conditioning can be distinct from the function that is utilised in learning for a spatial assignment [80] [81].

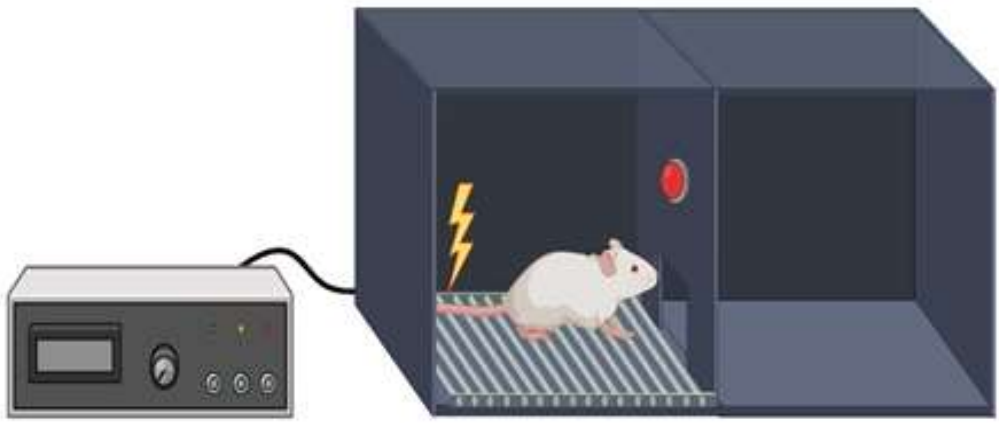

Fig 5: Fear Conditioning Chamber

Passive-Avoidance Learning

When doing the passive-avoidance learning task, the animal is required to learn how to avoid a somewhat unpleasant stimulus, which in this case is darkness.[82][83] This is accomplished by the animal remaining on the side of the apparatus that is well-lit and avoiding entering the dark, which is where it is exposed to the aversive stimuli. Fig. 6). Taking into consideration the fact that mice have a natural predisposition to draw towards darkness, it is necessary for the animal to resist this tendency by combining the negative stimulus with the compartment that it desires. Not only will animals that do not recall the unpleasant stimuli pass over earlier, but animals that do remember will also cross over earlier. Both the median step-through latency, which is the amount of time it takes for an animal to cross into the dangerous side, and the percentage of animals from each experimental group who are able to pass the threshold within the allotted amount of time are dependent measures [84,85.86].

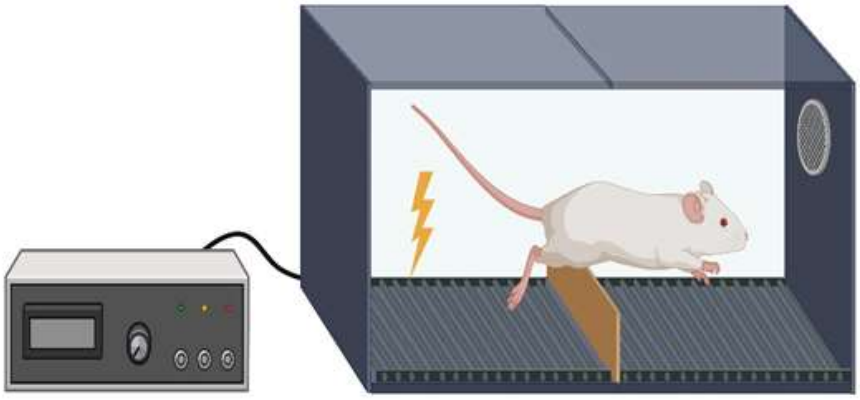

Fig: 6 Paaive Avoidance learning

Working Memory/Novelty/Activity

Y-Maze

This test is based on the natural tendency of mice to wander around with their arms alternated while they are exploring a new location.[87][88] There are many other variants available, each with a distinct level of difficulty and a different set of requirements applied to particular forms of cognition. When it comes to the investigation of cognitive alterations in Alzheimer's disease transgenic animals, the spontaneous alternation form of the Y-maze is one of the versions that is very well-liked. As an example, test animals are placed in a labyrinth in the shape of a Y for a period of six to eight minutes. During this time, the number of arms that are entered, as well as the sequence in which they are entered, are recorded, and a score is computed to determine the alternation rate, which is the degree to which the arms are entered without repetitions. With a high alternation rate, animals are able to demonstrate sustained cognition because they are required to remember which arm was entered most recently in order to avoid entering it again [89][90]

A variation of the Y-maze that is designed to test short-term memory can also be carried out. In this form, one arm of the Y-maze is blocked, and the subject is given the opportunity to explore both arms for fifteen to thirty minutes. Following this, the animal is withdrawn from the maze for a period of time ranging from a few minutes to many hours, depending on the experimental modification. After this, the animal is reintroduced into the maze, but this time with all of its arms open, and allowed to explore for a period of five minutes. Animals who have retained their cognitive function will remember the arm that was blocked during the first trial, and they will enter that arm first during the second trial.[91][92] In order to assess the animal's long-term memory as well as the amount of time it takes for the animal to relearn the task, this test can also be repeated one week after the previous trial was completed, with only two minutes of delay time in between each attempt. When it comes to measuring parameters, the first arm that is entered, the length of time that is spent in each arm, and the total number of arm entries are typically included [93].

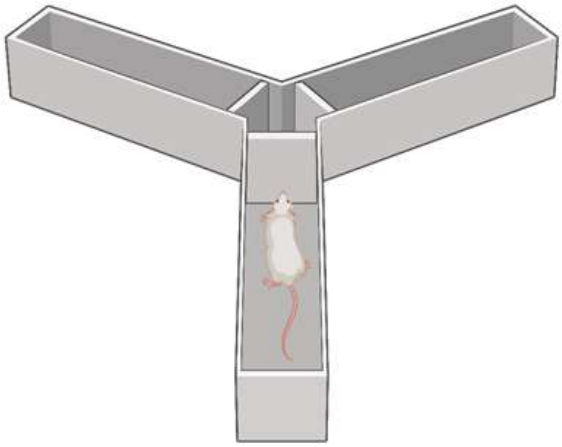

Fig: 6 Y- Maze test

T-Maze

There is a significant amount of application for T-maze activities in the field of cognitive behavioural testing in both mice and rats. These tasks are quite well characterised. The animals are began at the base of the T, and they are given the opportunity to select one of the goal arms that is adjacent to the opposite end of the stem (figure 7). The mouse has a tendency to select the arm that it has not previously visited on the second trial, which is a reflection of its memory of the initial choice. This occurs when two trials are presented in rapid succession. The term for this phenomenon is "spontaneous alternation." It is possible to foster this propensity by encouraging the animal to get hungry and then rewarding it with a food that it prefers if it alternates between the two. However, other brain regions are also involved in the process. Both spontaneous and rewarded alternations are extremely sensitive to dysfunctions in the hippocampus, and as a result, they are vulnerable to symptoms that are similar to those of Alzheimer's disease. It is expected that each trial will be finished in less than two minutes; however, the total number of trials that will be necessary will vary depending on the statistical and scientific criteria [94].

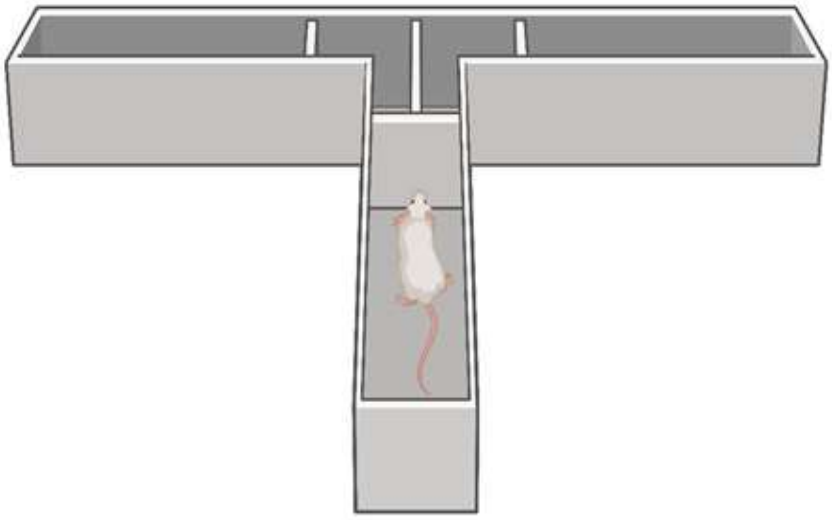

Fig: 7 T- Maze Test

Object Recognition

The object identification test is based on the inherent predisposition of rats to study a new object rather than a familiar one, as well as their innate tendency to restart investigating when they are given with a new environment.[95] This is the basis for the test. It is clear that learning and recognition memory processes are being utilised, as evidenced by the decision to investigate the unfamiliar object and the subsequent reactivation of exploration following the displacement of the object. The object-recognition tasks that are available for testing

cognition in rats make use of a variety of various configurations, as well as a variety of different numbers of available objects and surroundings in which the animals are evaluated. All of these configurations are designed to assess a variety of different things, including spatial recognition and novelty. There is a specific object identification task that is extremely suitable for testing Alzheimer's disease-related deficiencies [96-97]. This task is sensitive to age-related shortcomings. figure 8 shows. A mouse is placed in a circular open field that is filled with diverse things (i.e., various plastic toys of different sizes and shapes) for a period of twenty-five minutes in order to complete this assignment. During the course of a series of tests, during which the animal has become accustomed to the arrangement and characteristics of the various objects, a selection of the objects is moved from one position to another in order to evaluate the animal's ability to recognise spatial relationships. [98][99]After that, some of the objects are changed out for new ones in order to get a better understanding of how novel objects are recognised. Calculations are made regarding the amount of time spent investigating the wide field (by moving around or remaining inactive), as well as the number of times and the amount of time spent inspecting each object across the several trials[100][101].

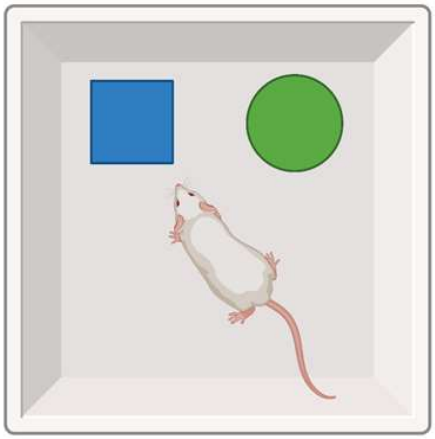

Fig: 8 Object recognition test

Open Field

The open field locomotion test is largely utilised for the purpose of evaluating motor function through the measurement of spontaneous activity in an open field. There are distinct quadrants or parts that are divided into the open fields, which can be either circular or square in shape and vary in size depending on the experiment.[102][103][104] After the animal has been placed in the open field, the movements of the animal are either videotaped or watched by computer systems that are automated. Rearing, line crosses, cleaning, overall movement, the number of lines crossed, predilection for particular parts, and/or faecal motions are all things that can be calculated in order to investigate behaviour and anxiety [105,106].

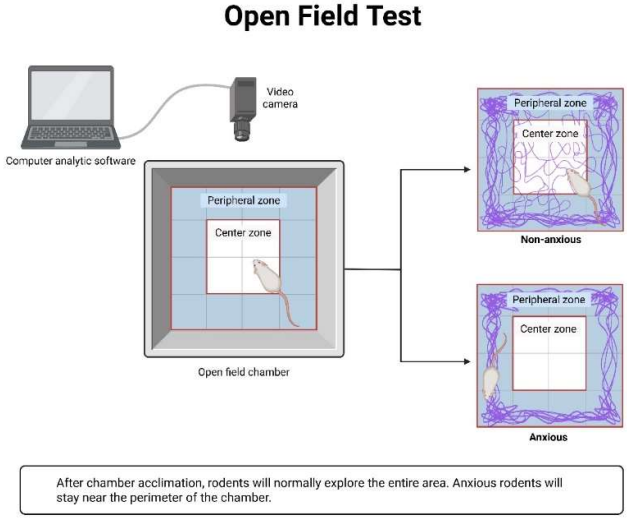

Fig: 9 Open field Test

APP (Amyloid Precursor Protein) Mutation-Based Mice

The production of amyloid deposits in the extracellular parts of the brain is one of the primary characteristics of Alzheimer's disease, and these models are based on having this characteristic. Many of these models are based on the transgenic overexpression of human amyloid precursor protein (APP), which is paired with various familial Alzheimer's disease-associated mutations in the APP gene. This combination results in the synthesis of various amyloid peptides that assemble more easily [107,108,109]. Overexpression of amyloid precursor protein (APP) was chosen as the way to simulate the β-amyloidosis that is characteristic of Alzheimer's disease (AD) brains. This specific method generates high quantities of β-amyloid. However, it also results in higher levels of APP fragments, including sAPP, CTF-α, CTF-β, and AICD, which are known to induce some unfavourable consequences [110]. Later on, a new generation of mouse models based on APP mutations, known as knock-in mice, was developed in order to address this issue. These mice had high levels of β-amyloid, but they did not have APP overexpression or the side effects that are associated with it [111-114]. For the purpose of Alzheimer's disease (AD) research, various APP mutation-based models have been established since the 1990s. These models are based on distinct mutations within the APP gene that are associated with different promoters. Each of these models depicts a different aspect of the disease as well as a varied expression time, as shown in figure 10.

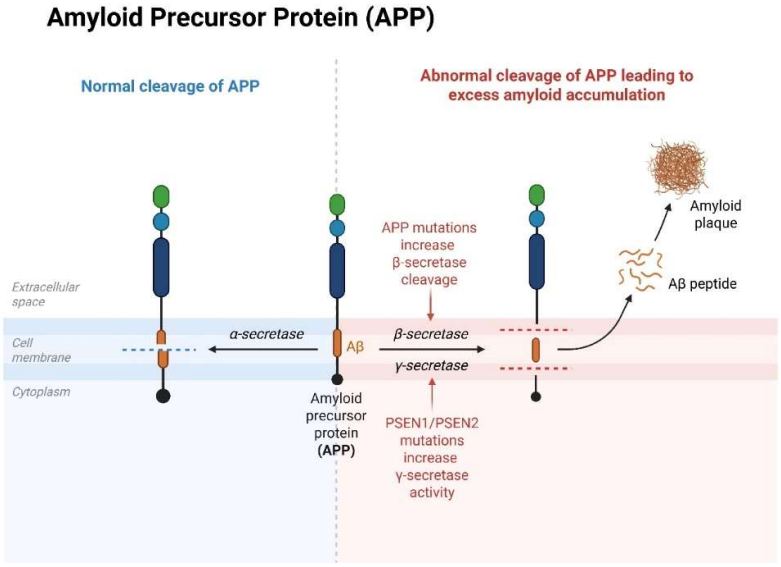

Fig: 10. **APP (Amyloid Precursor Protein) Mutation-Based Mice**

PDAPP Model

Using the PDGF-β promoter, the PDAPP model was the first mouse model established for Alzheimer's disease (AD). This model was developed by overexpressing the human APP gene with the Indiana mutation (V717F) discovered in the early 1990s. This mutation involves the substitution of a valine for a phenylalanine at the 717th position of the APP gene. When the animal is roughly 6–9 months old, this model begins to produce extracellular β-amyloid deposits. These deposits continue to rise as the animal ages, demonstrating an age-dependent progression with regional specificity in the brain, which is comparable to the trend seen in Alzheimer's disease patients [115][116][117]. PDAPP animals also exhibit dystrophic neurites, a decrease of synaptic and dendritic density, and enhanced gliosis [118]. These findings are in addition to the first observation. In terms of behavioural problems, these mice exhibit acute impairments in a radial maze test beginning at the age of three months. Additionally, they have a lower performance in object recognition, which develops in a manner that is dependent on the age of the mouse and is believed to be connected with memory impairment [119].

Tg2576 Model

Overexpressing the human APP695 gene with the Swedish mutation (KM670/671NL) discovered in the early 1990s, Tg2576 is the second rodent model of Alzheimer's disease that has been created and is one of the most widely utilised models by researchers. In this model, a lysine is replaced with an asparagine at the residue 670, and a methionine is replaced with a leucine at the residue 671. The hamster prion promoter is used to make these substitutions [120-125]. As per the findings of Games et al. [126], this particular model exhibits a noteworthy

rise in the accumulation of β-amyloid deposits at approximately 11–13 months of age when compared to controls of the same age who have a distribution pattern that is equally distributed. Simultaneously, Tg2576 mice display dystrophic neurites, a decrease in synaptic and dendritic density, and an activation of microglial-mediated inflammatory response in and around β-amyloid plaques, accompanied by an increase in the number of participants [126]. When compared to behavioural problems, these mice exhibit learning and memory impairment around the age of nine months, with age-dependent aggravation, as determined by the Y and water maze tests [127].

APP23 Model

The human APP751 gene is overexpressed in APP23 mice, which are characterised by the Swedish mutation (KM670/671NL) and the utilisation of the murine Thy1 promoter [128]. Beginning at the age of six months, this particular model begins to exhibit the development of β-amyloid deposits, which gradually increase in size and quantity as the animal ages. These deposits are primarily found in the regions of the neocortex and the hippocampus [129]. Furthermore, it is worth noting that these mice have dystrophic neurites, a glial response in which microglia and astrocytes are observed in the vicinity of β-amyloid plaques, and for the first time, neuronal death occurs around the age of 14 months [130,131]. There is a significant decrease in the density of pyramidal neurones in the CA1 region of the hippocampus, as well as in the piriform and entorhinal cortices; however, there are no comparable changes in the neocortex portion of the brain [134]. In terms of behavioural disturbances, APP23 mice exhibit cognitive decline, characterised by significant learning and memory deficits, beginning at the age of three months. This decline is associated with the progression of ageing, even before the β-amyloid deposition was evaluated using a Morris-type water maze test. Additionally, these mice exhibit perturbations in their circadian rhythms and activities, which are also observed in Alzheimer's patients [135]

J20 Model

With the combination of two known mutations, the Swedish mutation (KM670/671NL) and the Indiana mutant (v717F), J20 mice are able to overexpress the human APP gene. This is accomplished by the utilisation of the PDGF-β promoter, as stated in reference [136]. After three months of age, this particular model begins to exhibit diffuse β-amyloid deposition. However, J20 mice do not exhibit plaque formation until approximately seven to nine months of age, primarily in the region of the hippocampus. This demonstrates that the expression of these peptides is dependent on the age of the mice [55,56]. These mice likewise display neuronal loss from the hippocampal CA1 area promptly at three months of age, with intensified advancement through ageing, accompanied by inflammation with astrogliosis and microgliosis peaking at six months of age [137]. In addition to this, these mice exhibit progression that is accelerated through ageing. As far as behavioural problems are concerned, J20 mice exhibit hyperactivity and spatial memory impairments as early as four months of age, as demonstrated by a radial arm maze test. These deficits and hyperactivity got more severe as the mice aged [138]. With the use of this model, conclusions were able to be disregarded regarding the dependence of the neurodegenerative process on the deposition of β-amyloid plaque. This is because neuronal death, inflammation, and behavioural impairment all began much before the formation of β-amyloid plaque [139].

TgCRND8 Model

Overexpression of the human APP695 gene, which encodes both the Swedish (KM670/671NL) and the Indiana (V717F) mutations, is achieved by TgCRND8 mice through the use of the hamster PrP gene promoter [140]. This particular model has a high rate of diffuse β-amyloid deposition, followed by the formation of β-amyloid plaques, which can be identified as early as three months of age and undergo rapid progression with increasing age [141,142]. At the same time, these animals display dystrophic neurites that are encircling plaques, as well as a focal and quick inflammatory response with microglial cells. This is then followed by astrocytic gliosis, and there is also some neuronal loss in the stratum pyramidale of the CA1 hippocampal region [143,144,145]. In terms of behavioural disturbances, it has been observed that TgCRND8 mice exhibit impairments in spatial learning and memory beginning at three months of age, concurrently with the development of β-amyloid plaques. These impairments were evaluated through the use of water maze and object recognition tests. Additionally, these mice exhibit deficits in sustained attention, which have also been documented in Alzheimer's patients [146,147].

App^{NL-G-F} Knock-In Mice Model

In contrast to the other mice, the AppNL-G-F Knock-In mice express the mouse APP gene, as opposed to the other mice, in which the β-amyloid sequence was humanised in order to prevent the overexpression of the human APP gene [148]. As is the case with the human APP gene, this mouse APP gene also incorporates mutations. These include the Swedish mutation (KM670/671NL), the arctic mutation (E693G) discovered in the early 2000s, where a glutamic acid is substituted with a glycine at the residue 693 (which is located within the β-amyloid region of APP), and the Iberian mutation (I716F) discovered in the early 2010s, where phenylalanine is substituted for

an isoleucine at the residue 716 [149]. Despite the fact that plaques were only observed at the age of 6 months, this model demonstrates aggressive β-amyloidosis. The presence of cortical β-amyloid deposition is recognised by the age of 2 months, and it reaches practically saturation by the age of 7 months. Furthermore, the density of plaques continues to increase until the age of 9 months [150]. In addition to this, synaptic damage is discovered in the prefrontal cortex between the ages of three and four months, and it worsens in a manner that is age-dependent, eventually spreading to the hippocampus between the ages of six and eight months [151]. According to [152], neuroinflammatory reactions such as microgliosis and astrocytosis can be identified as early as six months of age. In terms of behavioural disturbances, AppNL-G-F Knock-In mice exhibit some learning and memory impairment beginning at the age of 6–9 months, with an age-dependent progression. This impairment was evaluated using the Morris water maze, Y maze, Barnes maze, object recognition test, and fear conditioning test. Additionally, the elevated plus maze test also revealed anxiolytic-like behaviour beginning at the age of 6 months [153-155].

CONCLUSION

The Wistar rat model induced by amyloid-beta ($A\beta_{142}$) peptide injection into the hippocampus has proven to be a reliable and reproducible system for studying Alzheimer's disease (AD). This model effectively mimics key aspects of AD pathology, including amyloid plaque deposition, neuronal degeneration, and cognitive impairments. Behavioral assessments such as the Morris Water Maze (MWM), Y-maze, and passive avoidance tests have consistently demonstrated significant deficits in spatial learning, working memory, and associative learning, respectively, thereby validating its utility in preclinical research. The consistent manifestation of AD-like symptoms in this model underscores its potential for evaluating therapeutic interventions. For instance, studies have shown that compounds like vinpocetine can ameliorate cognitive deficits in $A\beta_{142}$-infused rats by reducing oxidative stress and enhancing neuroprotection . Similarly, thymoquinone has been reported to mitigate cognitive impairments and neuronal damage through its antioxidant properties Moreover, integrating this model with modern techniques like optogenetics, gene editing, and advanced imaging could enhance our understanding of AD pathophysiology and facilitate the development of more effective treatments. While challenges remain in translating preclinical findings to clinical success, the Wistar rat model continues to be an invaluable tool in the quest for effective therapies for Alzheimer's disease

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