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ANIMAL MODELS OF CHEMICAL-INDUCED ALZHEIMER'S DISEASE: AN OVERVIEW

Rashda Khatoon, Vanita G. Kanase *, Abhaykumar Yadav, Nitesh Gupta, Shivam Varma and Sayali Shete

Department of Pharmacology, Oriental College of Pharmacy, Navi Mumbai - 400705, Maharashtra, India.

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Correspondence to Author:
Dr. Mrs. Vanita G. Kanase

HOD,
Department of Pharmacology, Oriental College of Pharmacy, Navi Mumbai - 400705, Maharashtra, India.

E-mail: rashdask121095@gmail.com

ABSTRACT: Characteristics like dementia, behavioural and cognitive dysfunction, and memory decline may characterize Alzheimer's disease (AD). A deterioration of short-term memory, inability to acknowledge new information, mood swings, difficulty recognizing words, forgetting names, and losing things are demonstrated by early disease. Popular emotional characteristics displayed by patients with AD are anger, aggression, and irritability. Today's world attempts to treat various ailments have increased with medical advancements. There is still considerable research into medications capable of preventing or at least effectively altering the trajectory of AD, referred to as 'disease-modifying medicines. Laboratory animals are helping to test new ways of treating illness. For the goal of developing therapeutics or disease-modifying agents, a vast array of experimental models were developed to simulate the human context of the illness. In animal studies, AD caused by chemical compounds may be helpful in deeper understanding the mechanism of disease and AD treatment. The anticholinergic drug Scopolamine induces amnesia in rodents. This analysis examines the various animal models frequently used to research the effect of novel drugs or medicinal herbs on chemical-induced Alzheimer's disease, such as scopolamine. This article provides an explanation of behavioral testing and the assessment of brain enzyme levels.

INTRODUCTION:

Neurodegenerative Diseases: A common and increasing cause of morbidity and mortality, particularly in the elderly, is a degenerative brain disease (ND). While they often have overlapping symptoms, the specific neurodegenerative diseases are diverse in their clinical manifestations and inherent anatomy [1]. Diagnostic Degenerative brain diseases are characterized by progressive cell malfunction, often affecting particular neuronal pathways, indicating some form of targeted susceptibility.

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The main fundamental processes that can be observed in several various stages of neuronal circuits, ranging from cellular to systemic, like neurodegeneration, are considered multifactorial, triggered by genomic surroundings, Ageing-related biological and hereditary factors [2].

Alzheimer's disease: Alzheimer's dementia is a degenerative brain disorder that could be categorized by behavioral deterioration and memory loss, concentration deficiency, and a gradual reduction in linguistic efficiency. Many factors can trigger AD, including congenital abnormalities, neurofibrillary tangle development, impaired processing of amyloid progenitors, mitochondrial deficiencies, neurotrophic factor deficiency, neurotoxicity of trace elements, defective of energy metabolism, as well as oxidative damage [3]. A depletion of short-term memory, failure to learn

new knowledge, mood changes, difficulty recognizing terms, forgetting identities and losing things are demonstrated by earlier illness. Frustration, aggression, and irritability are typical emotional characteristics displayed by AD patients [4].

Alzheimer's disease symptoms progress from mild symptoms of memory impairment to extremely serious dementia. The coexistence of vascular dysfunction and Alzheimer's disease is progressively medically, pathologically, and epidemiologically acknowledged [5]. Alzheimers disease is the world's most prevalent kind of dementia that makes up 60 percent-80 percent of all cases of dementia, affecting an estimated 24 million individuals worldwide [1].

Most cases of AD have the normal, predominantly amnestic kind, whereas up to 15% of cases are regarded atypical, with earlier or significant perceptual, frontal, motor, or other manifestations. Based on pathological, molecular, and congenital evidence that supports the importance of this compound in the illness process, the amyloid-βeta protein has become a significant therapeutic focus in AD. In preclinical models of Alzheimer's disease, Amyloid βeta immunotherapies were found to reduce the overall cerebral Aβ concentrations and enhance cognitive function [6].

Different techniques are used to diagnose Alzheimer's disease, such as: psychological evaluations, examination of mental condition and neuropsychological evaluation, lab testing, brain scans, Computerized tomography, MRI, PET, Positron emission tomography (pet, CSF examination, electroencephalogram (EEG), electromyogram [5]. Therefore, clinical therapy of Alzheimer's disease aims to improve patient signs and optimize the standard of living of the patient and the care provider [1]. Donepezil, Galantamine, Memantine, Rivastigmine, Memantine + Donepezil are widely used agents authorized by the US FDA for the therapy of Alzheimer's disease. Therapies able to block or at least efficiently altering the course of Alzheimers, attributed as 'disease-modifying medications, are all under deep analysis [7].

Animal Models: In AD studies, animal experiments play a key role. For the objective of generating therapies or disease-modifying agents, a broad array of animal experiments have been conducted to simulate the human framework of the disorder. In real sense, the first objective of most preclinical studies is to mimic the neuropathological observations of AD accompanied by a cognitive function association without determining whether neuropathological agents in animal and human studies have analogous biological implications [8].

These animal models would not precisely create the anatomical manifestations of the illness in the individual mind, but it is biochemically quite comparable. [9]Pharmaceutical companies obviously need to determine the acceptability of the inherent principle in the development stage prior to actually beginning costly studies. Contributing factors can emerge from modeling of animals [10]. Compared to varying models, with respect to learning and motor activities, neuroanatomy and the endocrine system, mouse models are known to be much stronger than invertebrates [9].

Genetically engineered animals and natural animal models of Alzheimer's are used for preclinical study of Alzheimer's Disease. Currently, to acknowledge the progression of this illness, these animal models could be utilized to mimic Alzheimer's pathology. In an attempt to comprehend the more complicated tissue-specific pathologies, numerous *in-vitro* methods are created too [11]. Spontaneous, chemical-induced, transgenic, and other miscellaneous methods can be categorized into animal studies for AD. After injecting an appropriate drug such as streptozocin, colchicine, Amyloid-beta proteins, ethanol, scopolamine, *etc*., the drug-induced Alzheimer's disease model involves disease progression [9].

This study will address the Scopolamine-induced AD models in depth. Scopolamine is an antagonist of the muscarinic cholinergic receptor used in laboratory animals for memory impairment. Researchers have demonstrated scopolamine-induced memory failure due to oxidative brain damage. Scopolamine-induced modeling is therefore used to screen for anti-dementia drugs in experimental animals [3]. The memory loss caused by scopolamine is commonly used due to the non-involvement of any surgical procedures [9].

Scopolamine Induced AD Models:
***In-vivo* Methods (Behavioural Tests):**

1. Morris water maze test
2. Elevated plus maze test
3. Social recognition test
4. Y- Maze test
5. Hebbs William Maze
6. Novel object recognition test
7. Passive avoidance paradigm

***In-vitro* Methods (Biochemical Tests):**

1. Estimation of Acetylcholinesterase enzyme levels in the brain
2. Determination of catalase principle
3. Superoxide dismutase assay
4. Glutathion reductase assay
5. Glutathion peroxidase assay

Morris Water Maze Test: The MWM comprises a water-filled round pool [(26±1) °C]. The pool is split into 4 imaginary quadrants labelled N, S, E, W. An escaping platform is positioned and entombed 1 cm underneath the liquid layer inside any of the four maze quadrants (the target quadrant), and it is not relocated through the procedure [12]. The animal must be positioned in one of the quadrants for the water maze learning and allowed to swim/hunt for the platform for a duration of 60 sec. Halt the stopwatch when the rodent enters the platform, and note the time. If the platform can't be identified in 120 seconds, then record the time as 2 min for this trial.

Utilize non-fat powdered milk or 125 ml of non-toxic white tempera paint to produce opaque water to commence the experiment with the Morris water maze. Position the Rodent in the pool and track the movements of the Rodent and note the time it takes before it reached the stage. The investigator should direct it to the target, as in training, if the rodent does not hit the platform in 2 min. Let them sit for Ten secs anyways, and afterward dry them off and place the rodent back in their cage [13]. As an indicator of learning, the Escape Latency Time (ELT) to spot the secret stage in the water maze is reported [12].

Elevated Plus Maze Test: The elevated plus maze for rodents consists of two open arms (16 cm × 5 cm) and two concealed arms (16 cm × 5 cm × 15 cm) extending from the centralized stage (5 cm × 5 cm) and raising the labyrinth from the ground to a height of 25 cm. Every mouse is positioned on the distant end of an open arm on the first day, heading away from centralized from the central stage. Transfer latency (TL) is described as the time spent by the animal with all its 4 limbs to shift from the open arm into any of the concealed arms. TL is registered for every animal on the first day (*i.e*., the 10th day of administering drugs.

If within 90 sec the organism did not reach any of the closed arms, it is softly forced into any of the 2 closed arms, and TL is allocated as 90 sec. The rodent is allowed for a further 120 seconds to start exploring the maze and then transferred to its native environment. 24 h (11^{th} day), later to the test, the preservation of this acquired task (memory) is checked [14].

Social Recognition Test: Wistar rats (male) can be utilized for the studies, and for social stimulation, juvenile males can be employed. A juvenile rat is inserted into the cage of an adult male on the commencement day of the research, and the time spent by the adult male in social investigative activity is documented within a defined period of 5 mins, and 24 h from this exposure, either the same juvenile or an unknown one is again inserted in the mature male cage, and social investigative activity is recorded for a 5-mins [15].

As compared to T1, a substantial decrease in social contact time in T2 is regarded as good learning. The index of recognition (RI=T2/T1) must be determined [12].

Y-Maze Test: For chronically stressed rats, the Y-maze task can be an efficient spatial memory test since behavioural evaluation can be initiated a day following the final stress session and completed within hrs after its beginning. When the cumulative acts of stress are at their height, the evaluation of spatial recognition-memory from the output of the Y maze will indicate the deterioration in the hippocampus. The utility of the Y maze as a test of cognition and integrity of hippocampus and spatial recognition still hasn't been established, however. To determine absolute functioning spatial memory, a type of short-term memory, the Y-maze test is used.

The Y-maze is a horizontal maze of three arms (120° apart). The rodents are initially positioned in any of the 3 arms. For each animal, the arm entry pattern and the no. of arm entries are manually registered during 8 min. An alternation is described consecutively as an entry in all 3 arms (for example, BAC, CBA, or ACB). The animal is administered with the experimental drug or standard treatment 60 min prior to the Y-maze study, and 30 min later, memory failure is produced by scopolamine administration. Animal control is only administered with the vehicle. The below mentioned equation specifies the percent alternation: percent alternation = [(total no. of alternations)/ (total arm inputs-2)] ×100 [16].

Hebbs William Maze: Hebbs maze is an extero-ceptive behavioral method focused on reward, beneficial for testing rodent spatial functioning memory. The major components of HWM are (i) the organism compartment connected to (ii) the central/ exploratory compartment and (iii) the incentive compartment at the other end of the labyrinth in which the incentive (food) is stored. With guillotine detachable doors, all three components are supported. The rodent is put in the organism compartment on the commencement day of experimentation, and the door is removed to allow the entrance of the animal into another compartment. Instantly after the animal passes into the next compartment, the door of the organism compartment is blocked so that back intervention is prevented.

On the first day, the learning index represents the time needed by the rodent to enter the incentive compartment (TIC) from the organism compartment. Until transferring to the home cage, each rodent is given the opportunity to explore the maze for 3 mins with all the gates opened. 24 h since the first trial, persistence (memory score) of this learned task is tested. An efficient decrease in the value of TIC depicts cognitive enhancement [17].

Novel Object Recognition Test: The Novel Object Recognition experiment is employed in animal models of neurological disorders to assess memory, particularly memory recognition. This test is based on rodents' spontaneous propensity to invest most time investigating an unfamiliar object than a known one.

The decision to explore the unfamiliar object represents the utilization of memory for learning and identification. In an incredibly simple enclosure, with or without a transparent wall, a recognition experiment is carried out. The process consists of three entirely separate phases: a phase of habituation, a phase of acquisition, and a phase of retention.

On 1st day (a phase of habituation), rats are made to perform a 10-min familiarization activity individually, during which they'll be placed into the blank space to become familiar with the procedure.

Animals would then attend a 10min test next day (a phase of acquisition), 2 objects (A & B) positioned in an extremely rhombohedral location within the world's center line were installed upon the floor. 10 cm apart and 8 cm from the nearest wall (each object should be roughly 5 cm in size). Made from an analogous substance of the same colouring and scent, the 2 objects must be entirely variable in shape but similar in size. Rodents are permitted inside the open field to start exploring the artifacts. The exploring time is represented (in secs) on each item to indicate the rodents' exploring activity.

Rodents are permitted to explore the open field in the existence of 2 items on the 3rd day (phase of retention): the familiar object A and a totally new object C (A & C) are of identical color and scale, different shapes.

For every rodent, a recognition index (RI) (phase of retention) is measured as the ratio: RI = Time exploring novel object / 100% (Time exploring novel object + Time exploring familiar object) [18].

Passive Avoidance Paradigm: The long-term cognition is tested using Passive Avoidance Actions based on negative feedback. The assembly comprises of a container (27 cm × 27 cm × 27 cm) with three wooden walls and one Plexiglass wall, with a grid floor (composed of 3 mm stainless steel tubes set 8 mm away), with a wooden stage in the center of the grid floor (10 cm × 7 cm × 1. 7 cm).

During the experiment process, the container is lighted with a 15W lamp. The electrical stimulation is transmitted to the grid floor. At first, the rodents are conditioned and placed carefully on the wooden deck set in the middle of the grid floor. Shock is

generated for 15 seconds when the rodent moves down to put all its legs on the grid floor, and the step-down latency (SDL) is registered. The time required (in seconds) by the rodent to pull back from the wooden platform to the grid floor with all its paws on the grid floor is known as SDL. For the acquisition and retention test, organisms displaying SDL in the range of 2–15 sec during training are employed.

90 minutes after the practice phase, the acquisition task is performed. Rodents are excluded from the shock-free zone during the acquisition test if they've not stepped down for a time of 60 sec. Retention is similarly assessed after 24 h, except that electrical shocks are not introduced to the grid floor with an upper cut-off time of 5 min. Enhancement in cognition is demonstrated by a substantial increase in SDL value [15].

***In-vitro* Methods (Biochemical Tests):**

Preparation of Brain Sample: Rodents from every group are euthanized using a carbon dioxide chamber after evaluating the neurocognitive paradigms in scopolamine-induced memory impairment; the brains are rapidly withdrawn and put in ice-cold saline. On a petri plate frozen on crushed ice, the frontal cortex, hippocampus, and septum (and any other parts of interest) are immediately dissected. The tissues are weighed and homogenized in a phosphate buffer of 0.1M (pH 8). Separate test tubes are used to keep the samples of brain homogenates from rodents. For enzymatic assays, the supernatant is being utilized [18].

Estimation of Acetylcholinesterase Enzyme Levels in the Brain (Ellman Method): This technique is completed by UV Spectrophotometry. Acetylthiocholine iodide is employed as a substrate for the calculation of cholinesterase activity (1 mM final concentration of acetylthiocholine iodide). The same day, substrate solutions are produced and utilized (with ice). The mentioned steps are included in this process.

1. Estimate the enzyme by UV spectrophotometery. The time for the analysis is 5 min, and the working temp is set at 25 °C. In each case, by subtracting the rate of absorbance of reagent blank, (*i.e.* without sample) the rate of absorbance increase can be corrected.

2. Determine the cholinesterase activity by using a 13.6 mM^{-1} cm^{-1} extinction coefficient for 5-thio-2-nitrobenzoate.

3. For brain: Cholinesterase activity= (Change in absorption x Micromol × Reaction size ml) / (Min × 13.6 × Sample size ml × tissue weight gm.) =Micro mol/min/g.[19]

For brain: Behavior of cholinesterase = (Change in absorption × micromole × size of reaction ml)/ (Min* 13.6* sample size ml* weight of tissue gm.) = Micro mol/min/g. H2O2 shows a continuous increment in absorbance with a decrease in wavelength in the UV range [19].

Catalase Principle: The deterioration of H2O2 can be directly followed by a 240 nm fall in absorbance. A measure of the catalase principle is the change in absorbance per unit.

Observation: Verify absorbance at the interval time of (0, 15, 30, 60, and 120 sec.)

Procedure: Catalase is calibrated according to the Claiborn *et al.* process. A cuvette containing 1.9 ml of 50 mM phosphate buffer was added with 0.1 ml of supernatant (pH 7). 1 ml freshly prepared 30 mM H_2O_2 is introduced to this buffer solution. The extent of H_2O_2 breakdown is measured by UV spectroscopy at 240 nm. Catalase values are represented as n moles of H_2O_2 per min per milligrams of protein consumed [20].

Superoxide Dismutase Assay: The enzyme superoxide dismutase in all oxygen metabolising cells is vital for life. It is present in the mitochondria of multicellular organisms within cytosol and intermembrane space. There is copper and zinc in it. This radical is indeed the hydrogen peroxide precursor in normal cells. The superoxide (O2-) is scavenged by SOD, and thus a first-line defense against free radical damage is produced. SOD belongs to metalloenzymes that produce H_2O_2 & molecular oxygen by catalyzing dismutase superoxide anion in the following manner.

$$2H_2O_2 + 2O^- \rightarrow 2\ H_2O + O_2$$ [20]

SOD activity could be calculated using the Kakkar *et al.* process. Reaction mixture comprises 0.1 ml phenazine methosulphate 186 micro-M, 1.2 ml, pH 7.0 sodium pyrophosphate buffer 0.052 mM, 0.3 ml

supernatant liquid after centrifugation (1500* g, 10 min further at 10,000* g, 15 min) of tissue homogenate 10%. This reaction mixture has a final volume of 1.6 ml. 0.2 ml of 780 µM NADH is added into the mixture to commence the enzyme reaction. After 60 sec, 1 ml of glacial acetic acid is added to halt the enzyme reaction. SOD activity can be determined at a wavelength of 560 nm and expressed as U/mg of protein [21].

Glutathion Reductase Assay: To analyse the GSR operation as per Carlberg & Mannervik process1.65 ml (0.1M) phosphate buffer, pH 7.6, 0.1 ml (0.5mM) EDTA, 0.1 ml (0.1mM) NADPH, 0.05 ml (1mM) oxidised GSH including 0.1 ml (10%) brain homogenate is used in reaction mixture. Reaction mixture has a volume of 2.0 ml. Changes in reaction mixture absorption (*i.e.,* NADPH disappearance) at 25 °C is measured at a wavelength of 340 nm and represented as nM NADPH of oxidized/min/mg of protein by using the extinction coefficient (in molars) of 6.22×10^3 M^{-1} cm^{-1} [21].

Glutathion Peroxidase Assay: The performance of GSH-Px is calculated as per Mohandas *et al.,* process eaction mixture includes 1.49 ml (0.1M) pH 7.4 phosphate buffer & 0.1 ml (1mM) sodium azide, 0.05 ml (1IU/ml) glutathione reductase solution, 0.05 ml (1mM) GSH, 0.1 ml (1 mM) EDTA, 0.1 ml (0.2 mM) NADPH, 0.01 ml (0.25 mM) H_2O_2, including 0.1 ml (10%) homogenate of the brain. The volume of reaction mixture is 2.0 ml. Changes in reaction mixture absorption (NADPH disappearance) at 25°C are measured at a wavelength of 340 nm that can be represented by nM NADPH (oxidized/min/mg) of protein by using an extinction coefficient (in molars) 6.22×10^3 M^{-1} cm^{-1} [21].

CONCLUSION: Alzheimers Dementia is a degenerative brain disease that can be described by behavioural deterioration and memory loss, concentration deficiency, and a gradual reduction in linguistic ability. A depletion of short-span memory, failure to understand new knowledge, mood changes, difficulty to remember words, difficulty in recalling names, & losing things are demonstrated by early illness. Widely known emotional characteristics displayed by patients having Alzheimer Disease are anger, aggression, including irritability.

Most of the cases of Alzheimer Disease show the amnestic form, i.e., typical, while around 15% of cases are atypical, with earlier or significant visual, frontal & motor including other symptoms. Donepezil, Galantamine, Memantine, Rivastigmine, Memantine, + Donepezil are widely used medications authorized by US FDA for the management of Alzheimer's disease.

There is still considerable research into medications capable of preventing or at least effectively altering the progress of the Alzheimer' dementia, which is referred as the 'disease-modifying medicines. In AD science, the Role of animal experiments is very significant. To establish therapies or the disease-modifying substances, a wide variety of experi-mental methods have been generated to replicate the human complexity of the illness. Such animal experiments may not precisely generate the anatomical manifestations of the illness in human brain, but they are very similar biochemically.

Compared to different models, in the case of memory & motor functions, neurophysiology and endocrinology, mouse models are found to be far better than invertebrates. After administering a suitable chemical compound such as streptozotocin, colchicine, Aβ protein, alcohol, scopolamine, *etc*., the chemically induced AD model requires disease growth. Scopolamine is an antagonist of the muscarinic cholinergic receptor that is used in laboratory animals for cognitive dysfunction. Because in the non-involvement of any surgical procedures, scopolamine-induced amnesia is commonly used.

Among the various behavioural approaches widely used models of Anti-Alzheimer's study on rodents are the MWM test, Elevated plus maze method, Social recognition model, Y- Maze study, Hebbs William Maze, Novel object recognition model, passive avoidance paradigm, etc. Estimation of acetylcholinesterase enzymes in brain, assessment of the catalase, estimation of malonyl dialdehyde, measurement of nitric oxide, Superoxide dismutase assay, Glutathione reductase assay, Glutathione peroxidase assay are some of the biochemical studies.

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memory from the output of the Y maze will indicate the deterioration in the hippocampus. Hebbs maze is an exteroceptive behavioral method focused on reward, beneficial for testing rodent spatial functioning memory.

The novel object recognition experiment is employed in animal models of neurological disorders to assess memory, particularly memory recognition. This test is based on rodents' spontaneous propensity to invest more time investigating an unfamiliar object than a known one. The long-term cognition is tested using Passive Avoidance Actions based on negative feedback.

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