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Experimental Models for Evaluating Learning and Memory: A Neuropharmacological Perspective

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ABSTRACT

Learning and memory are essential cognitive processes that rely on complex neuronal interactions and are often impaired in neurodegenerative and psychiatric disorders. To study these mechanisms, a variety of animal models and behavioral paradigms have been developed. This paper reviews exteroceptive and interoceptive models, including mazes, passive and active avoidance tasks, electroshock-induced amnesia, hypoxic stress, and pharmacological assays. These models are widely employed to assess memory acquisition, retention, and retrieval, as well as to evaluate potential therapeutic agents. Understanding such models provides valuable insights into memory processes and offers translational relevance for developing novel treatments for cognitive impairments.

KEYWORDS: Learning, Memory, Animal models, Cognitive function, Behavioural assays

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INTRODUCTION

Learning is the process by which new information is acquired. The following retention of the information is referred to as memory, which is the process by which acquired knowledge is kept. Learning is described as the learning of information and skills [1].

Both a psychological process and a change in synaptic brain connectivity can be thought of as aspects of learning and memory. Cognitive behaviour is mostly composed of learning and memory1. However, memory loss, strange behaviour, personality changes, and eventually death are all symptoms of Alzheimer's disease, a neurodegenerative brain ailment that progresses gradually [2]. Memory, judgement, orientation, understanding, learning ability, and language are among the many cortical functions that are disrupted in this chronic, progressive, and debilitating organic brain disorder [3].

The brain is the organ that is responsible for what we call the mind. It is the basis for thinking, feeling, wanting, perceiving, learning and memory, curiosity, and behaviour. Memory is a fundamental mental process, and without memory we are capable of nothing but simple reflexes and stereo type behaviours [4]. Thus, learning and memory is one of the most intensively studied subjects in the field of neuroscience. Memory is a faculty by which sensations, impressions, and ideas are stored and recalled,

where learning is a process by which brain acquires new information about the events occurring in the given surroundings [5]. Learning and memory are complex phenomenon requiring the coordinated interaction of multiple brain structures. The diencephalon, a subcortical region that includes the thalamus and hypothalamus, has been characterized as an integral connection zone for many memory-related circuits. There are connections between the thalamus and the hippocampus, as well as the amygdala and striatum. All three of those regions (hippocampus, striatum, amygdala) are important for different types of memory [6].

Animal models are very beneficial for our understanding of the psychological and physiological underpinnings of many disease states [7,8].

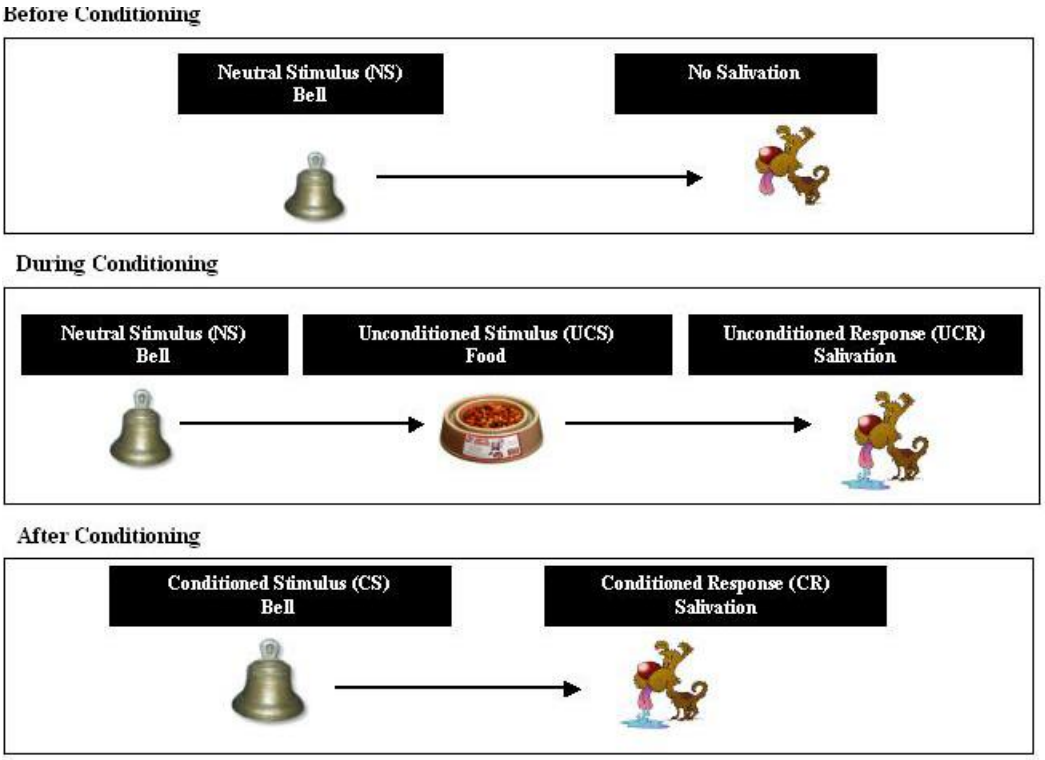

Figure 1: Classical Conditioning: Learning through Association

Various Behavioural and Pharmacological Models Currently Available for the Evaluation of Learning & Memory Processes:
I. Exteroceptive Aversive Stimuli Models
a. Behaviour on mazes

- Elevated plus -maze
- Radial arm maze
- Y-maze
- Figure-8 maze
- Morris water maze
- Modular mazes
- Stone T-maze

b. Passive avoidance

- Step-down type passive avoidance test
- Modified passive avoidance test

c. Active Avoidance

- Two way active avoidance test

II. Interoceptive Aversive Stimuli Models
a. Electroshock-induced amnesia
b. Hypoxic stress-induced learning deficits
c. Pharmacological and discrimination

EXTEROCEPTIVE AVERSIVE STIMULI MODELS

Behaviour on Mazes

Elevated Plus Maze: The elevated plus maze served as the exteroceptive behavioral model (wherein the stimulus existed outside

the body) to evaluate learning and memory in mice [8]. The apparatus consisted of two open arms and two covered arms the arms extended from a central platform and the maze was elevated to a height from the floor. On the first day, each mouse was placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) was taken as the time taken by the mouse to move into any one of the covered arms with all its four legs. TL was recorded on the first day. If the mouse did not enter into one of the covered arms within 90 s, it was gently pushed into one of the two covered arms and the TL was assigned as 90 s. The mouse was allowed to explore the maze for 10 s and then was returned to its home cage. Memory retention was examined 24 h after the first day trial on the second day.[9]

RADIAL ARM MAZE TASK PERFORMANCE

Locally fabricated wooden radial arm maze elevate 50cm above the floor consist of an octagonal central hub 36cm in diameter with eight radial arms. Each arm is 43 cm long, 15 cm wide with 12 cm sides and has small black plastic cups mount at 30cm from the central hub. Each mouse maintain at 85% of its total diet, is exposed to the maze daily with the food pellet in a fix arm followed by respective drug treatment for the period of 07 days. The apparatus is cleaned with damp cloth after each trial to avoid place preference and the influence of olfactory stimuli. The evaluation is carried out on 7^{th} day, 60 minutes after the respective drug treatment where in a food pellet is placed in a variable arm for evaluation of working memory. Each mouse place on the central hub is allowed to choose any of the arms freely to get the food. Latency to find food is recorded as a measure of working memory evaluation11. The comparison is made against the vehicle treated control group and the data is expressed as mean ± SEM.[10]

Morriz Water Maze: Morris water maze was employed to evaluate learning and memory . It consists of a circular water tank (diameter 150 cm and height 45 cm), filled with water maintained at 25°C. The water is made opaque with a white colored dye. The tank is divided into four equal quadrants with the help of two threads, fixed at right angle to each other on the rim of the pool. A platform (10 cm2) of 29 cm height is located in the center of one of these four quadrants. The position of platform and clues were kept consistent throughout the training session.

Acquisition trials: Each animal was subjected to four consecutive trials on each day with an interval of 5 min, during which mouse was allowed to escape on the hidden platform and was allowed to remain there for 20 sec. In case of the inability of the animal to locate the hidden platform within 90 sec, it was gently guided by hand to the platform and allowed to remain there for 20 sec. Escape latency time (ELT) to locate the hidden platform in water maze was noted as an index of acquisition and learning. In preliminary study, trial was conducted to familiarize the mice with the task and was not counted. Mouse was subjected to acquisition trials for four consecutive days. Starting position on each day to conduct four acquisition trials was changed as follow:
Day 1 Q1 Q2 Q3 Q4
Day 2 Q2 Q3 Q4 Q1
Day 3 Q3 Q4 Q1 Q2
Day 4 Q4 Q1 Q2 Q3

Retrieval trial : On the next day, platform was removed and each mouse was allowed to explore the pool for 90 s. Mean time spent of the animal in each of four quadrants was noted. The mean time spent by the mouse in target quadrant for searching the hidden platform was noted as an index of retrieval. The experimenter always stood at the same position. Care was taken that relative location of water maze with respect to other objects in the laboratory, serving as prominent visual clues was not disturbed during the total duration of study [11].

Passive Avoidance

Passive avoidance task is fear-aggrevated test used to evaluate learning and memory in rodent models of CNS disorder [11]. One of the most common animal tests in memory research is the inhibition to imitate activities or learned habits. The term “passive avoidance” is usually employed to describe experiments in which the animal learns to avoid a noxious event by suppressing a

particular behaviour [12].
Step-down Passive Avoidance Test: Passive-avoidance behavior based on negative reinforcement was recorded to examine long-term memory. Each mouse was gently placed on the wooden platform set in the center of the grid floor. When the mouse stepped down and placed all its paws on the grid floor, shocks were delivered for 15 s and the step- down latency (SDL) was recorded. SDL was defined as the time taken by the mouse to step down from wooden platform to grid floor with its entire paw on the grid floor. Mice showing SDL in the range (2–15 s) during the first test were used for the second session and the retention test [13]. The second session was carried out 90 min after the first test. When mice stepped down before 60 s, electric shocks were delivered for 15 s. During the second test, animals were removed from shock free zone if they did not step down for a period of 60 s. Retention was tested after 24 h in a similar manner, except that the electric shocks were not applied to the grid floor. Each mouse was again placed on the platform, and the SDL was recorded, with an upper cut off time of 300s [13,14] Step-through Passive Avoidance Test: The apparatus (BPT Co., Tehran) consisted of an illuminated chamber connected to dark chamber by a guillotine door. Electric shocks were delivered to the grid floor by an isolated stimulator. On the first and second day of testing, each rat was placed on the apparatus and left for 5 min to habituate to the apparatus. On the third day, an acquisition trial was performed. Rats were individually placed in the illuminated chamber. After a habituation period (5 min), the guillotine door was opened and after the rat entering the dark chamber, the door was closed and an inescapable scrambled electric shock (1 mA, 1 s once) was delivered. In this trial, the initial latency (IL) of entrance into the dark chamber was recorded and rats with ILs greater than 60 s were excluded from the study. Twenty-four hours later, each rat was placed in the illuminated chamber for retention trial. The interval between the placement in the illuminated chamber and the entry into the dark chamber was measured as step through latency (STL up to a maximum of 600 s as cut-off) [15] Active Avoidance The active avoidance task is a fear-motivated associative avoidance test based on electric current as a source of punishment. In this task the mouse has to learn to predict the occurrence of an aversive event based on the presentation of a specific stimulus, in order to avoid the aversive event by actively moving to a different compartment. The measures recorded, number of avoidances (the mouse crossing to the other compartment during the stimulus signal), number of non-responses (the mouse failing to cross to the other compartment during the trial), response latency (latency to avoid or escape), serve as an index of learning and allows memory to be assessed [16].

Shuttel Box Active Avoidance Test: Shuttle box avoidance is a more difficult task. Since the animal is not handeled between trials, the shuttle box can be easily automated [18]. In this apparatus consist of a rectangular chamber divided into 2 compartments. Both compartments are lighted by overhead stimulus lights. The two compartments are separated by an automatic guillotine door and each has a grid floor through which a foot shock can be delivered. On first day of experiment (habituation day) a mouse is placed in one of the two compartments and allowed to ambulate freely between the two compartments of the shuttle box for 10 minutes in order to become familiarized with the learning environment. On the next day (training day) a mouse is placed in one of the two compartments and allowed to ambulate freely between the two compartments of the shuttle box for 1 minute (lights are on in both compartments). After 1 minute the light, used as the conditioned stimulus (CS), is switched off in the compartment in which the mouse is in, and 5 seconds later, a foot shock is delivered (unconditioned stimulus (US), 0.3mA, 5 second duration). The shock and light co-terminate such that the light is on for 10 seconds. If the mouse fails to make a response, both CS and US are terminated after 5 seconds of foot shock. During inter trial intervals, mice are permitted to move freely and to cross back and forth between compartments. The next trial always starts in the compartment where the mouse was located at the end of the ITI.[17] Runway avoidance Mice or rats of either sex are used and maintain under standard conditions and handle for several days before the experiment. The same box as use in the step-through model can be use in this experiment. The apparatus is uniformly illuminated by an overhead light source. A loudspeaker, mount 50 cm above the start-box, serves for presenting the acoustic condition stimulus (CS; an 80 dB, 2000 Hz tone from an audio generator). The foot shock is employed by the same source as in the step-through avoidance. The animal is allowed to explore the whole apparatus for 5 min. The guillotine door is then close and the animal is place into the light starting area. After 10 s the acoustic CS is applied and the door is simultaneously open. Shock is turned on after 5 s. The CS continuous until the animal reaches the safe area. It is left there for 50-70 s (intertrial interval, ITI) before return to the same area again. The procedure starts again. The training is continued until the animal attains the criterion of 9 avoidances in 10 consecutive trials. On the next day the procedure is repeated until the same learning criterion is reached and finally the time need to reach the safe area is measured [18]

INTEROCEPTIVE AVERSIVE STIMULI MODELS

Electroshock Induced Amnesia

In the electroshock induced amnesic models retrograde amnesia is induced by the electric shock. The memory loss effect of this method is due to the electric shock rather than the convulsion . The rats were trained to run into the enclosed chamber of either the left or the right arm of a T-maze; a food pellet served as a reward in the correct arm. Arm assignment was random and was retained unchanged for each rat to the end of the study; the number of left-and right-arm rats was equal in the treatment groups. Satisfactory learning was defined as nine correct arm entries over 10 consecutive trials on the maze. On each of four consecutive days, the rats were trained to the criterion for satisfactory learning. Two learning measures were recorded; the number of trials to satisfactory learning and the number of trials with wrong arm entries. T-maze training was conducted between 10 AM to 3 PM.
On the fifth day, rats were randomised to receive true or sham ECS. True ECS was administered through saline-soaked ear clip electrodes using the Electro con MK II 50 Hz sinusoidal wave ECT device (Associated Electronics Engineering, Bangalore, India). The stimulus settings were 130 volts x 0.5 sec. Sham ECS involved identical handling without passage of current. True/sham ECS were administered at approximately 10 AM and again at approximately 3 PM on the same day. The motor seizure duration (in the true ECS groups) and the subsequent spontaneous righting time were recorded by an experienced observer using a stopwatch. The motor seizure was defined to extend from the commencement of passage of current to the commencement of asymmetrical/asynchronous limb activity or the cessation of movement, whichever occurred earlier. Righting time was defined as extending from the termination of the motor seizure to the spontaneous righting to an erect posture upon all four limbs. On the

day after ECS, the rats were reassessed on the T-maze until satisfactory learning was attained. Learning measures, reflecting efficiency of recall of pre-ECS learning, were recorded as before. ECS was expected to impair recall (BR-16A).[19] Hypoxic Stress-induced Learning Deficits Animals were housed in eight identical commercially designed chambers (30×20×20 in) that can accommodate six rats each and are operated under a 12-hour light–dark cycle (Oxycycler model A44XO; Reming Bioinstruments, Redfield, NY). Gas was circulated around each of the chambers, attached tubing, and other units at 60 L/min (i.e., one complete change per 30 s). The O2 concentration was continuously measured by an O2 analyzer and was changed throughout the 12 hours of light time (6:00 A.M. to 6:00 P.M.) by a computerized system controlling the gas valve outlets, such that the moment-to-moment desired oxygen concentration of the chamber was programmed and adjusted automatically. Deviations from the desired concentration were met by addition of N2 or room air (RA) through solenoid valves. For the remaining 12 hours of night time, oxygen concentrations were kept at 21%. This specific and validated profile consists of 90 seconds of 10% O2 alternating with 90 seconds of RA for 12 hours during the light phase, and typically results in nadir PaO2 of 37 to 42 mm Hg and oxyhemoglobin saturations ranging from 68 to 76%. Ambient CO2 in the chamber was periodically monitored and maintained at 0.03% by circulating the gas through soda lime. The gas was also circulated through a molecular sieve (Type 3A; Fisons, East Grinstead, UK) to remove ammonia. Humidity was measured, and was maintained at 40 to 50% by circulating the gas through a freezer and silica gel. Ambient temperature was kept at 22 to 248C. After 12 weeks of either NA or PA, rats werestarted on the IH protocol for 14 days, after which water maze experiments were initiated and IH exposures continued until completion
of all maze procedures [20].

Pharmacological & Discrimination Assays

Scopolamine-Induced Amnesia: The administration of the antimuscarinic agent scopolamine to young human volunteers produces transient memory deficits [21]. Analogously, scopolamine has been shown to impair memory retention when given to mice shortly before training in any behaviour task [22,23.24,]. The ability of a range of different cholinergic agonist drugs to reverse the amnesic effects of scopolamine is now well documented in animals and human volunteers. However, the neuropathology of dementia of the Alzheimer type is not confined to the cholinergic system [24].

The scopolamine test is performed in groups of 10 male NMRI mice weighing 26–32 g in a one-trial, passive avoidance paradigm. Five min after i.p. administration of 3 mg/kg scopolamine hydrobromide, each mouse is individually placed in the bright part of a two-chambered apparatus for training. After a brief orientation period, the mouse enters the second, darker chamber. Once inside the second chamber, the door is closed which prevents the mouse from escaping, and a 1 mA, 1-s foot shock is applied through the grid floor. The mouse is then returned to the home cage. Twenty four hours later, testing is performed by placing the animal again in the bright chamber. The latency in entering the second darker chamber within a 5 min test session is measured electronically. Whereas untreated control animals enter the darker chamber in the second trial with a latency of about 250 s, treatment with scopolamine reduces the latency to 50 s. The test compounds are administered 90 min before training. A prolonged latency indicates that the animal remembers that it has been punished and, therefore, does avoid the darker chamber. Using various doses latencies after treatment with test compounds are expressed as percentage of latencies in mice treated with scopolamine only. In some cases, straight doses-response curves can be established whereas with other drugs inverse U-shaped dose-responses are observed [25]. Sodium Nitrite Induced Amnesia*:* Sodium nitrite induced amnesia is a type of Interoceptive aversive stimuli model. The manipulation of brain metabolism was used to show the beneficial effects of substances which influence learning and memory. [26], during investigations of sodium-nitrite (NaNO2) on brain metabolism, demonstrated a close relationship between oxidative metabolism and cholinergic function. From the results of their studies, the possibility cannot be excluded that an induction of impairment of the cholinergic transmission in addition to a deficiency in brain metabolisms was induced [27] Substantial impairment of cognitive functions such as mental skill, vigilance memory, logical reasoning and psychomotor performance has been observed at altitude above 3000m. Brain structures are most vulnerable to the oxidative stress especially hippocampus which is involved in memory. Reduced partial pressure of oxygen at high altitude causes oxidative stress by forming reactive oxygen and nitrogen species (RONS), which attack lipid, protein, DNA and activate the downstream pathway, leading to neuronal damage. The neuronal damage may finally lead to impairment in memory function [28]. Different authors have followed different procedures to induce chemical hypoxia and evaluate learning and memory using step-down apparatus. Various studies suggested that sodium nitrite at a dose of 75mg/kg by subcutaneous route showed learning and memory impairment [25].

CONCLUSION

Animal models of learning and memory play a crucial role in understanding cognitive functions and testing therapeutic agents. These experimental approaches provide translational insights into mechanisms of memory impairment and hold promise for advancing treatment strategies in neurodegenerative and psychiatric disorders.

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Conflict of Interest

No conflict of interest were found

Author's contribution

All the authors have contributed equally completing this manuscript.

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