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Review Article

VARIOUS ANIMAL MODELS TO CHECK LEARNING AND MEMORY - A REVIEW

AVNEET GUPTA[1,2*], HEMRAJ[1,2], SUNNY JALHAN[2], ANIL JINDAL[2], NEERAJ UPMANYU[3]

[1]Department of Pharmacy, CMJ University, Shillong, Meghalaya, India, [2]L.R. Institute of Pharmacy, Rajgarh Road, Solan, HP, [3]R.K.D.F College of Pharmacy, Bhopal, MP, India. Email: avneet3083@gmail.com

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ABSTRACT

Various animal models have played a major role in the history of modern drug development for memory. Models for Alzheimer's disease complement human investigations to study in detail pathogenic hypothesis and therapeutic strategies. To achieve this several new models have been produced. Various methods have been applied to induce in animals experimental models of memory which would provide important insight into the aetiopathogenic mechanism of human memory. The present study is therefore focused on discussing such animal models.

Keywords: Animal models, Learning and Memory, Alzheimer's disease.

INTRODUCTION

Learning is defined as the acquisition of information and skills or in other words it is the process by which new information is acquired and subsequent retention of the information is called memory, which is the process by which acquired knowledge is retained. Learning and memory can be conceived as both a psychological process, as well as change in synaptic neural connectivity. Learning and memory are the basic constituents of cognitive behavior[1]. But Alzheimer's disease is a progressive neurodegenerative brain disorder that occurs gradually and results in memory loss, unusual behavior, personality changes and ultimately death[2]. It is a chronic, progressive disabling organic brain disorder characterized by disturbance of multiple cortical functions, including memory, judgment, orientation, comprehension, learning capacity and language[3]. To overcome the problem of Alzheimer more effective drugs must be evaluated in a proper way to insure their better effectiveness. This can only be possible if suitable animal models would be selected. The present study is therefore focused on discussing different animal models for Learning and memory.

MODELS FOR LEARNING AND MEMORY

Inhibitory (Passive) avoidance

Passive avoidance behavior based on negative reinforcement is recorded to examine long-term memory. The apparatus consisted of a box (27 × 27 × 27 cm) having three walls of wood and one wall of Plexiglas, featuring a grid floor (3 mm stainless steel rods set 8 mm apart), with a wooden platform (10 × 7 × 1.7 cm) in the center of the grid floor. The box is illuminated with a 15 W bulb during the experimental period. Electric shocks (20V AC) deliver to the grid floor. Training performs in two similar sessions. Each mouse is gently placed on the wooden platform set in the center of the grid floor. When the mouse step down and place all its paws on the grid floor, shocks are delivered for 15 sec and the step-down latency (SDL) is recorded. SDL define as the time taken by the mouse to step down from wooden platform to grid floor with its entire paw on the grid floor. Animals show SDL in the range (2-15 sec) during the first test used for the second session and the retention test. The second-session is carried out 90 min after the first test. When the animals step down before 60 sec, electric shocks are delivered for 15 sec. During the second test, animals are removed from shock free zone if they do not step down for a period of 60 sec. Retention is tested after 24 h in a similar manner, except that the electric shocks do not applied to the grid floor. Each mouse is again placed on the platform and the SDL is recorded, with an upper cut-off time of 300 sec[4,5,6].

Elevated plus maze (EPM)

The elevated plus maze serve as the exteroceptive behavioral model (wherein the stimulus existed outside the body) to evaluate learning and memory in mice. The apparatus consist of two open arms (16 cm × 5 cm) and two cover arms (16 cm × 5 cm × 12 cm). The arms are extended from a central platform (5 cm × 5 cm) and maze is elevated to a height of 25 cm from the floor. On the first day, each mouse is placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) is the time taken by the mouse to move into any one of the cover arms with all its four legs. TL is recorded on the first day. If the animal does not enter into one of the covered arms within 90 sec., it is gently pushed into one of the two covered arms and the TL is assign as 90 sec. The mouse is allowed to explore the maze for 10 sec and then return to its home cage. Memory retention is examined 24 h after the first day trial on the second day[7,8,9].

Morris water maze test

The Morris water maze consist of a large circular black pool of 120 cm diameter, 50 cm height, filled to a depth of 30 cm with water at 26±2 °C. Four equally space points around the edge of the pool is designed as N (North), E (East), S (South) and W (West). A black color round platform of 8 cm diameter is placed 1 cm below the surface of water in a constant position in the middle of the NE quadrant in the pool; the starting point is SW quadrant in all the trials. The water is colored with non-toxic black dye to hide the location of the submerged platform. The rat could climb on the platform to escape from the necessity of swimming. Trials are given for 3 consecutive days in order to train rat with a maximum time of 120 s (cut-off time) to find the hidden platform and is allowed to stay on it for 30 s[10]. The experimenter put the rat that fail to locate the platform onto it on first session. The animals are given a daily session of 5 trials per day. Latency time to reach the platform is recorded in each trial.

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 7th 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 evaluation[11]. The comparison is made against the vehicle treated control group and the data is expressed as mean ± SEM.

Barnes circular maze test

The maze consist of a white acrylic disc (122 cm in diameter) that is elevated 90 cm above the floor and contain 40 holes, each 5 cm in

diameter, equally space around the perimeter of the circle. One of the holes led to a black Plexiglas escape tunnel (5 x 5 x 11 cm). To familiarize mice with the maze and the existence of the escape tunnel, they are subjected to two habituation sessions on two consecutive days (one session per day). The position of the tunnel is varied randomly from mouse to mouse but remains constant throughout testing for a given mouse. Each mouse is placed in the middle of the maze under a start chamber (a square black box) and a buzzer (80 dB) and light is turned on. After 10 sec, the chamber is lifted and the mouse is guided to the escape tunnel. When the mouse enters the escape tunnel, the buzzer and light is turned off and the mouse is allowed to remain in the tunnel for 1 min. On the following 18 days, actual test trials (one trial per day) are performed under identical conditions, except that the mice need to locate the escape tunnel by themselves. Each trial ends when the mouse enters the goal tunnel or after 5 min has elapse. The amount of time that the mice take to enter the tunnel (escape latency) and the number of errors (define by the animal placing its nose in a hole that do not lead to the escape chamber) are recorded for each trial.

One month after the last training trial, the mice are retested to evaluate memory retention. The position of the target hole is the same as during the training period. One week after memory retention testing, the escape tunnel is moved to a new position opposite of the original (reversal learning). Mice are then subjected to five consecutive trials to locate the new position of the escape hole using the same procedure as described above[12,13,14].

T-maze delayed alternation task

The delay alternation test is conduct in a black plastic T-maze (stem, 38 x 9 cm; arms, 30 x 9 cm; walls, 15 cm high). Sliding doors separate the first 14 cm of the stem as the starting compartment and the arms from the stem 10 cm from the inter section. The end of each arm contained a small black plastic cup (1 cm in diameter) into which a food reward could be place. A variety of fixed extra maze clues surround the apparatus.

Mice are kept on a maintenance diet throughout the course of all T-maze experiments. This diet result in a weight loss of approx 10% after 2 days and approx 15% after the first week of dieting. This reduce weight is maintained throughout all subsequent experiments. After 2 days of dieting, animals are subjected to three 10 min adaptation sessions (one session per day for three consecutive days), during which they are allowed to freely explore the T-maze with all doors open and both arms bait with food (pieces of Froot Loop cereal; Kellogg's, Battle Creek, MI). On the day after the last adaptation session, mice are subjected to a force alternation protocol for five consecutive days (one session consisting of 11 trials per day; cutoff time, 10 min). The mice are forced (by blocking access to the previously visit arm) to visit one arm at the time, eat the food reward and return to the starting compartment. Mice are confined to the starting compartment for 5 sec between trials. For the initial trial, both arms are baited with food. The door leading into the straight alley is opened and the mouse is able to freely choose either the right or left arm of the T-maze and consume the food reward. The mouse is then allowed to return to the starting compartment. In the subsequent trial, the previously visit arm is blocked so that the mouse is forced to choose the previously no visit arm contain a food reward. This force alternation procedure is then repeated nine additional times.

Actual training sessions commence 1 day after the last force alternation session. In this case, animals are subjected to daily sessions (one session per day) consisting of 11 continuous trials (one initial trial follow by 10 test trials). On the first trial, both arms are baited. After the Actual training sessions commence 1 day after the last force alternation session. In this case, animals are subjected to daily sessions (one session per day) consist of 11 continuous trials (one initial trial followed by 10 test trials). On the first trial, both arms are baited. After the mouse has chose one arm and eat the food reward, the door to the unvisit arm is closed. The mouse is allowed to return the starting compartment alone and is confined there for 5 sec. During the following 10 trials, the food reward is always located in the arm not visit in the previous trial. A correct choice is made if the mouse enters the previously unvisit arm. The baited arm remains the same until visit, even if the mouse chose the incorrect arm repeatedly. These daily training sessions are continued for 18 d (intertrial interval, 5 sec). To set higher demands on working memory, the delay time (intertribal interval) is increased from 5 to 20 sec. Approximately 1 month after completion of the 5 sec task, the same set of animals are subjected for 10 consecutive days to the same training protocol as describe above.

The T-maze is cleaned with mild detergent and water between trials. The number (percentage) of correct choices (alternation rate) is recorded[15].

Step-down

Mice or rats of either sex are used. A rectangular box (50 × 50 cm) with electrifiable grid floor and 35 cm fits over the block. The grid floor is connected to a shock device which delivers scramble foot shocks. The actual experiments can be perform in different ways. A typical paradigm consists of three phases: (1) Familiarization: The animal is placed on the platform, release after raising the cylinder and the latency to descend is measured. After 10 s of exploration, it is returned to the home cage. (2) Learning: Immediately after the animal has descend from the platform an unavoidable foot shock is applied (Foot shock: 50 Hz; 1.5 mA; 1 s) and the animal is return to the home cage. (3) Retention Test: 24 h after the learning trial the animal is again placed on the platform and the step-down latency is measured. The test is finished when the animal steps down or remains on the platform (cut-off time: 60 s) and finally the time of descent during the learning phase and the time during the retention test is measured[16,17].

Step-through

Mice and rats of either sex are used. The test apparatus consists of a small chamber connect to a larger dark chamber via a guillotine door. The small chamber is illuminate with a 7 W/12 V bulb. The test animals are given an acquisition trial follows by a retention trial 24 h later. In the acquisition trial the animal is placed in the illuminate compartment at a maximal distance from the guillotine door and the latency to enter the dark compartment is measured. Animals that do not step through the door within a cut-off time: 90 s (mice) or 180 s (rats) are not use. Immediately after the animal enters the dark compartment, the door is shut automatically and an unavoidable foot shock (Foot shock: 1 mA; 1 s - mice; 1.5 mA; 2 s - rat) is delivered. The animal is then quickly remove (within 10 s) from the apparatus and put back into its home cage. The test procedure is repeated with or without drug. The cut-off time on day 2 is 300 s (mice) or 600 s (rats), respectively and finally the time to step-through during the learning phase is measure and the time during the retention test is measured[18,19].

Two compartment test

Mice and rats of both sex and a rectangular box with a 50 × 50 cm grid floor and 35 cm high walls are used. In the centre of one wall is a 6 × 6 cm opening connecting the large compartment to a small 15 × 15 cm box with dark walls, electrifiable grid floor and removable ceiling. The connection between the two compartments can be close with a transparent sliding door. Illumination is provided with a 100 W bulb place 150 cm above the centre of the large compartment and finally the times of animal spends in the large and the small compartment are measured[20,21].

Up-hill avoidance

Rats of both sexes are used and maintain under standard conditions. The experimental apparatus is a 50 × 50 cm box with 35 cm high opaque plastic walls. The box can be incline at different angles. The floor consists of 10 mm diameter stainless steel grid bars place 13 mm apart. To deliver the tail-shock, a tail electrode is constructed, consisting of a wire clip connect to a constant current shock source. The animal is first fit with the tail-electrode and then place onto the grid with its nose facing down. During baseline trials the animal's latency to make a 180° turn and initiate the first climbing response is measured. Thereafter the animal is returned to its home cage. During the experimental trials the latencies are measured and additionally tail-shock (1.5 or 2 mA) is administered contingent on

the first climbing response after the 180° turn. Immediately after the shock the animal is placed in its home cage. Retest is performed 24 h later and finally the latencies are measured[22].

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[23,24].

Shuttle box avoidance (two-way shuttle box)

Rats of both sexes are used and maintain under standard conditions. The apparatus consist of a rectangular box 50 × 15 cm with 40 cm high metal walls and an electrifiable grid floor. The box is divided by a wall with a manually or solenoid-operated guillotine door (10 × 10 cm) into two 25 × 15 cm compartments. Each compartment can be illuminate by a 20 W bulb mount in the hinge Plexiglas lids. A fix resistance shock source with an automatic switch (0.5 s on 1.5 s off) is use. Simple programming equipment provides for automatic delivery of the condition stimulus (CS) and the unconditional stimulus (US). The apparatus is placed in a dimly light room with a masking noise background (white noise) of 60 dB. The animal is allowed to explore the apparatus for 5 min with the connecting door open and the compartment lights switch off. The guillotine door is then close. After 20 s the light is switched on in the compartment containing the animal and the door is opened. A tone (CS) is present and 5 s later the floor shocks is applied in the illuminate compartment and continue until the animal escapes to the dark side of the compartment, the connecting door is closed and the shock discontinue. After a variable intertrial interval (ITI; 30-90 s) the light is switched on in the previous dark compartment, the door is open and the animal is required to cross to the other side. The training is continued until the animal reaches the criterion of 9 avoidances in 10 consecutive trials. Retention is tested at different intervals after the original training by retraining the animal to the same criterion again and finally the time of animal needs to reach the safe area on both days is measured. In addition, the numbers of errors (not reaching the safe area) are recorded[25].

Jumping avoidance (one-way shuttle box)

Rats of both sexes are used and maintain under standard conditions. The apparatus consists of a rectangular box 40 × 25 cm with 40 cm high metal walls, an electrifiable grid floor and a Plexiglas ceiling. A 12 × 12 × 25 cm opaque plastic pedestrial, mount onto one of the narrow walls of the box provides the isolate goal area. Flush with the horizontal surface of the pedestal moves a vertical barrier, which can either be retract to the rear wall of the apparatus to expose the goal area or push forward to block access to the goal completely. The animal is placed into the apparatus for 5 min with the goal area expose (barrier retract). The barrier is then move forwards and the goal is blocked for 2 s. The first trial starts by exposing the goal area and applying an acoustic CS (1000 Hz, 85 dB). Electric shocks - US (1.0 mA; 50 Hz; 0.5 s) are applied 5 s later (once per 2 s) and continue together with the CS until the animal jumps onto the platform. After 30 s the barrier pushes the animal off the platform onto the grid floor. The sequence is repeated until the criterion of 10 consecutive avoidances is reached. Retention is tested on the next day until the animal reaches criterion and finally the time of animal needs to reach the safe area on both days is measured. In addition, the number of errors (not reaching the safe area) is recorded[26].

Visual discrimination

Rats and mice of both sexes are used and maintain under standard conditions. The apparatus consists of a square 10 × 10 cm start area separate by a Plexiglas sliding door from the choice area, which is connected by swing doors to the goal compartment. The grid floor in the starting and the choice areas is electrifiable. The stimulus (mostly plastic cards 8 × 8 cm) can be attach to the swing doors. The patterns are black on a white background and have different forms. The apparatus is illuminated by a dim light. The animal is placed into the apparatus with all doors open and allows to explore it. Then it is place in the start and after 5 s release by raising the Plexiglas door. After another 5 s, electric shocks (1 mA, 50 Hz, 0.5 s, 1/3 s) are applied until the animal escapes through either of the open doors to the safe goal compartment where it is left for some seconds. As soon as this preliminary step is master, the stimulus cards are inserted, the negative door is locked and the grid section in front of this door is electrified. The animal is trained to a criterion. On the next day the animal is retrained to the same criterion and retention is expressed in savings. Another parameter which can be use to evaluate the savings is the cumulative numbers of errors until the criterion is reached and finally the number of correct answers as well as the number of trials until the criterion is reaches are counted[27].

Spatial habituation learning

The open-field apparatus is a rectangular chamber (rats: 60 × 60 × 40 cm, mice: 26 × 26 × 40) made of paint wood or grey PVC. A 25 W red or green light bulb is placed either directly above or beneath the maze to achieve an illumination density at the centre of approximately 0.3 lx. Masking noise is provided by a broad spectrum noise generator (60 dB). Prior to each trial, the apparatus is swept out with water containing 0.1% acetic acid. Housing room and the testing location are separated and animals are transported to the testing room 30 min before testing. The digitized image of the path taken by each animal is stored and analyze post hoc with a semi-automated analysis system (e.g. Ethovision, Noldus, The Netherlands or Truscan, Coulbourn Instruments, Allentown, PA). In aged or hypoactive rodents testing is performed during the animals dark phase of day. The rodent is placed on the center or in a corner of the open-field for 5-10 minute sessions (mice: up to 20 min, because of the high basal activity level). The animals are re-exposed to the open-field 24 and 96 h after the initial trial[28,29] and finally the exploratory behaviours register are: (1) Rearings or vertical activity: the number of times an animal was standing on its hind legs with forelegs in the air or against the wall. (2) The duration of single rearings as a measure of non-selective attention[30]. (3) Locomotion or horizontal activity: the distance in centimeters an animal move.

Spatial discrimination

Rats and mice of both sexes are used and maintain under standard conditions. The apparatus use is usually a simple T- or Y-maze, with an electrifiable grid floor. The last 10 cm of each arm are separated from the rest of the apparatus by a swing-door which prevents the animal from seeing the food cup or the plastic sheet covering the grid in the goal area. A fix resistance shock source is connected to an automatically operate switch. In an aversively motivate spatial discrimination learning the animal is trained to escape and/or to avoid foot shocks by always going to the right. Training starts by allowing the animal to explore the apparatus. Then the animal is placed on the start and after 5 s electric shocks (0.5 s, 50 Hz, 1.0 mA) are applied at 3 s intervals. The animals are trained to a criterion. On the following day the animal is retrained to the same criterion. After a 60 min interval the safe goal area is shifted to the other arm of the maze and the discrimination is reversed and finally Errors are scored. An error means that the animal enters the wrong arm with all four legs. During retention the numbers of trials until the animal makes correct choices are counted[31].

Olfactory learning

Rats (Sprague-Dawley or Long Evans) are generally used. Animals are deprived of water for 48 h before the training and during the test they receive ad libitum water for only 30 min. The olfactory apparatus is a rectangular box (30 × 30 × 55 cm) with a

photosensitive cell mount on top of the water spout/odor outlet. Rats are trained to approach the water spout and to break the light beam. Responses to the positive odor are rewarded with water while responses to the negative odor results in the presentation of a light flash. The intertrial interval before the presentation of a new odor is usually 15 s. and the sessions last 30 min. per day. Sessions are terminated when the rat makes 90% correct choices or after 400 trials and finally results are reported as the % correct responses or as a logit transformation of the % correct/incorrect response ratio[32,33].

Automated learning and memory model in mice

Naive male mice weighing 25-35 g are randomly assigned to experimental groups. They are housed at approximately 22°C at a 12:12 light/dark cycle with food and water continuously available. Twenty-four hours before each test, mice are isolated into individual cages and all food is removed. Water remains continuously available. Tests are conducted on two consecutive days. Mice are fed 1.5 g food immediately after the first session (day 1).

For experimental sessions, mice are place in sound attenuating enclosures containing specially design operant chambers (12.5 × 11 × 12.5 cm) equipped with a recess (dipper well; 2.2 cm diameter, 1.3 cm deep) for dipper accessibility on one wall of the chamber and two additional smaller holes (1.3 cm diameter, 0.9 cm deep) on either side of the dipper well. The dipper can be raise into the dipper well for a sucrose solution (110 g/1.0 l water) reinforcer presentation. Each recess has a photocell monitoring nose-poke responses. In addition, a speaker capable of sounding a stimulus tone is located on the wall opposite to the dipper and a house-light is on the ceiling. A computer and associate interface controls stimulus events and records nose-poke responses.

Five to nine mice per group are test in a 2 day procedure design to measure acquisition and retention of nose-poke response under an auto shaping schedule of reinforcement. Experimental sessions are conduct at the same time each day for 2 consecutive days. Both the acquisition session (day 1) and the retention session (day 2) are identical.

During the auto shaping procedure which is use to measure acquisition and retention of the response reinforcement for nose-poking a tone is add. This tone sounds on a variable-interval schedule of presentation (mean of 45 s, range 4-132) and stays for either 6 s or until a nose-poke in the dipper well is made before the end of the 6 s periods, at which time the tone is turn off and a dipper with sucrose solution is present. If a mouse fails to make a dipper well nose-poke during the tone, the dipper is automatically present at the termination of the tone. A dipper well nose-poke response made during the presence of the tone is count as reinforce response. Dipper well nose-poke responses made while the tone is off are count but have no consequence. Each session lasts for 2 h or until 20 reinforcers have been earn, whichever comes first. In addition to dipper well nose-poke responses, nose-pokes in the smaller holes to the left and right of the dipper are count but have no consequence.

Drugs in various doses or vehicle are administered i.p. immediately before the session. Rates of nose-poke responses made in the small holes on either side of the dipper well serve as a measure of general activity. The computer presents tones on a variable interval with a mean of 45 s and 10 possible intervals (4, 10, 15, 22, 29, 38, 49, 64, 87, 132 s) chose randomly without replacement until all intervals have been used. The latency of the response to the 10^{th} reinforcer is consider as a measure of acquisition and retention, because all mice have been expose to all possible intervals (in random order) by the 10^{th} tone. In order to eliminate the variance due to the variability of the first reinforcer, it is necessary to adjust any measure of acquisition and retention according to the response latency to the first reinforcer. The 10th response latency measure is thus adjust by subtracting the response latency to the first reinforcer (L-10-1) in order to ensure all mice have been exposed to the reinforcement contingency.

An other measure of acquisition and retention consists of the rate of nose-poke responding in the dipper well during the total session[34,35].

CONCLUSION

Different models to check memory enhancement were discussed in the present study. An attempt has been made here to collect all available information about the methods for nootropic activity which would enable the researchers to get all required informations about these methods at one place during their research.

REFERENCES

1. Kandel E. Learning and memory. Principle of neuroscience 2000; edition 4^{th}: 1227-1246.
2. Jewart R.D., Green J., Lu C.J., Cellar J., Tune L.E. Cognitive, behavioral and physiological changes in Alzheimer disease patients as a function of incontinence medications. Am J Geriatr Psychiatry 2005; 13: 324-8.
3. Katzman R., Kawas C. Risk factors for Alzheimer's disease. Neuro Science News 1998; 1: 27-44.
4. Joshi H., Parle M. Effects of piperine on memory and behavior mediated via monoamine neurotransmitters. J Trad Med 2005; 2: 39-43.
5. Parle M., Vasudevan M., Singh N. Swim everyday to keep dementia away. J. Sports Science and Medicine 2005; 4: 37-46.
6. Parle M., Dhingra D., Kulkarni S.K. Improvement of mouse memory by Myristica fragrans seeds: J Med Food 2004; 7: 157-61.
7. Dhingra D., Parle M., Kulkarni S.K. Memory enhancing activity of Glycyrrhiza glabra in mice. J. Ethnopharmacol 2004; 1: 361-5.
8. Itoh J., Nabeshima T., Kameyama T. Utility of an elevated plus maze for the evaluation of nootropics, scopolamine and electro convulsive shock. Psychopharmacology 1990; 101: 27-33.
9. Parle M., Dhingra D. Ascorbic acid: a promising memory enhancer in mice. J. Pharmacol. Sci 2003; 93: 129-35.
10. Morris R. Development of water maze procedure for studying spatial learning in the rat. J. Neurosci. Meth 1984; 11: 47-60.
11. Vyawahare N.S., Bodhankar S.L., Nikam A.P., Sharma R.G., Deshpande M.M., Tarnalli A.D. Effect of Clitoria ternatea extract on radial arm maze task performance and central cholinergic activity in rats. J Cell Tissue Res 2007; 7(1): 949-952.
12. Barnes C.A. Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. J Comp Physiol Psychol 1979; 93: 74-104.
13. Barnes C.A. Spatial learning and memory processes: the search for their neurobiological mechanisms in the rat. Trends Neurosci 1988; 11: 163-169.
14. Bach M.E., Hawkins R.D., Osman M., Kandel E.R., Mayford M. Impairment of spatial but not contextual memory in CaMKII mutant mice with a selective loss of hippocampal LTP in the range of the theta frequency. Cell 1995; 81: 905-915.
15. Crawley J.N. Behavioral phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioral tests. Brain Res 1999; 835: 18-26.
16. Jarvik M.E., Essmann W.B. A simple one trial learning situation in mice. Psychol Rep 1960; 6: 290.
17. Hudspeth W.J., McGaugh J.L., Thomson C.W. Aversive and amnesic effects of electroconvulsive shock. J Comp Physiol Psychol 1964; 57: 61-64.
18. Jarvik M.E., Kopp R. An improved one trial learning situation in mice. Psychol Rep 1967; 21: 221-224.
19. King R.A., Glasser R.L. Duration of electro convulsive shock induced retrograde amnesia in rats. Physiol Behav 1970; 5: 335-339.
20. Kurtz K.H., Pearl J. The effect of prior fear experience on acquired drive learning. J Comp Physiol Psychol 1960; 53: 201-206.
21. Bures J., Buresova O. Cortical spreading depression as a memory disturbing factor. J Comp Physiol Psychol 1963; 56: 268-272.
22. Staubli U., Huston J.P. Up-hill avoidance: A new passive avoidance task. Physiol Behav 1978; 21: 775-776.
23. Capaldi E.J., Capaldi E.D. Aversive learning situations: apparatus and procedures. In: Myers RD (ed) Methods in Psychobiology 1972; 2: 59-81.

24. Hock F.J., McGaugh J.L. Enhancing effects of Hoe 175 on memory in mice. Psychopharmacology 1985; 86: 114-117.
25. Netto C.A., Valente J.T., Borges S.J.B., Lasevitz J., Tomaz C.A. Reversal of retrieval impairment caused by retroactive interference in a two-way active avoidance task in rats. Behav Neur Biol 1991; 55: 114-122.
26. Tenen S.S. An automated one way avoidance box for the rat. Psychosom Sci 1966; 6: 407-408.
27. Thompson R. Localization of the 'visual memory system'in the white rat. J Comp Physiol Psychol 1969; 69: 1-29.
28. Thiel C.M., Müller C.P., Huston J.P., Schwarting R.K.W. High vs low reactivity to a novel environment: Behavioral, pharmacological and neurochemical measures. Neuroscience 1999; 93: 959-962.
29. Schwarting R.K.W., Sedelis M., Hofele K., Auburger G.W., Huston J.P. Strain dependent recovery of open field behavior and striatal dopamine deficiency in the mouse MPTP model of Parkinson's disease. Neurotox Res 1999; 1: 41-56.
30. Aspide R., Fresiello A., de Filippis G., Carnevale U.A., Sadile A.G. Non selective attention in a rat model of hyperactivity and attention deficit: subchronic methylphenidate and nitric oxide synthesis. Neurosci Biobehav Rev 2000; 24: 59-71.
31. Siegel S. Discrimination overtraining and shift behavior In: Gilbert RM, Sutherland NS (eds) Animal Discrimination Learning. Academic Press 1969; New York, NY, pp 187-213.
32. Eichenbaum H., Otto T., Cohen N.J. The hippocampus-what does it do? Behav. Neural Biol 1992; 57: 2-36.
33. Roman F.S., Simonetto I., Soumireu M.B. Learning and memory of odor-reward association: selective impairment following horizontal diagonal band lesions. Behav Neurosci 1993; 107: 72-81.
34. Vanover K.E., Barrett J.E. An automated learning and memory model in mice: pharmacological and behavioral evaluation of an autoshaped response. Behav Pharmacol 1998; 9: 273-283.
35. O'Connell M.F. Autoshaping and food acquisition in mice: a genetic analysis. J Comp Physiol Psychol 1980; 94: 1149-1159.