

Effects of post-training administration of LY341495, as a mGluR2/3 antagonist on spatial memory deficit in rats fed with high-fat diet

Heresh Moridi

Hamadan University of Medical Sciences Medical School

Abdolrahman Sarihi

Hamadan University of Medical Sciences Medical School

Elahe Habibitabar

Hamadan University of Medical Sciences Medical School

Hossein Shateri

Hamadan University of Medical Sciences Medical School

Iraj Salehi

Hamadan University of Medical Sciences Medical School

Alireza Komaki

Hamadan University of Medical Sciences Medical School

Jamshid Karimi

Hamadan University of Medical Sciences Medical School

Seyed Asaad Karimi (✉ asad_karimi_128@yahoo.com)

Hamadan University of Medical Sciences Medical School <https://orcid.org/0000-0002-8663-6485>

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Abstract

Background

High-fat diets (HFDs) adversely influence glutamate metabolism and neurotransmission. The precise role of the group II metabotropic glutamate receptors (mGluR2/3) antagonist on spatial memory deficit following consumption of HFD has not yet been clarified. Therefore, in this study, we examined the effects of post-training administration of mGluR2/3 antagonism; LY341495 on spatial memory in rats fed with HFD by using Morris Water Maze (MWM) task. Intraperitoneal injection (i.p) injection of LY341495 was done 30 minutes before retention test.

Results

Our results showed that HFD did not have any effect on memory acquisition. There were not significant differences in escape latency and swimming distance between experimental groups ($P > 0.05$, Two-way ANOVA). Our finding showed that consumption of an HFD leads to spatial memory impairment. There were significant differences in time spent in target zone between experimental groups [$F(3, 20) = 7.031$, $P = 0.0021$, one-way ANOVA]. Also, LY341495 improved HFD-induced reference memory impairment. HFD animals treated with LY341495 spent more time in the target zone in compare with HFD animals ($P = 0.0449$).

Conclusions

Our results suggested that prolonged consumption of high-fat diet has no effects on the acquisition of spatial learning, but can impair memory retention of the adult male rats and post-training administration of LY341495 can improve HFD-induced reference memory impairment.

Background

Despite the role of nutrients and foods in public health, information about the real effects of high-fat diet (HFD) on central nervous system (CNS) structure and function is still poor. Consuming a HFD has long been known to rise the risk of some diseases such as obesity, diabetes mellitus, metabolic syndrome, and also Alzheimer's disease and some types of cognitive impairment in humans and rodents (1). Although many studies repeatedly have shown that high-fat diet is associated with learning and memory impairment, it has recently been reported that high-fat diet improves memory in Wistar rats (2). These observations show a contradictory effect of high-fat diet on learning and memory. And it seems that further studies are necessary to clarify the issue. Thus, prospective studies evaluating the effects of HFD on cognitive functions are needed.

It is possible that HFD and obesity may induce cognitive disruption by impacting glutamate metabolism and neurotransmission. The glutamate actions are mediated by ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs respectively) (3–5). The iGluRs include N-methyl-D-aspartate (NMDA),

amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and kainate receptors. The mGluRs are G-protein coupled receptors and have eight subtype and are classified into three Groups (I (mGluR1 and mGluR5), II (mGluR2 and mGluR3), and III mGluR4, mGluR6, mGluR7, and mGluR8) depending on their signal transduction pathways, sequence homology, and pharmacological selectivity. It has been shown that HFD diets alter glutamate metabolism and neurotransmission in mice hippocampus and downregulates the NMDA receptor subunit NR2B (6). Also, in our previous work we examined the induction of long-term potentiation (LTP) under the blockade of the mGluR2/3 in the hippocampal perforant path- dentate gyrus (DG) pathway in rats fed an HFD (4). Interestingly we observed that blocking of group II mGluRs increased LTP in rats fed an HFD. These results indicated that mGluR2/3 inhibition may have stimulatory effects on LTP induction in the perforant path- DG pathway.

LTP is a major form of synaptic plasticity in the CNS, thought to underlie learning and memory (7) and has been reported that LTP is impaired by HFD consumption (8, 9). Modulation of glutamate transmission using compounds acting at mGluRs offers a hopeful way to investigate the role of the glutamatergic system in cognitive signs following consumption of HFD, and may promote the development of novel treatments for these cognitive impairments. mGluRs have a vital role in mediating glutamatergic system in the brain [3, 4]. Group II receptors are located mainly in presynaptic terminals (10) and are highly expressed in CNS areas related to learning and memory, such as the hippocampus, amygdala, and prefrontal cortex (PFC) (11, 12). Moreover, cognitive enhancement has been observed after treatment with metabotropic glutamate receptor 2/3 antagonists and glutamatergic blockade in some studies (13, 14). The present study therefore further explored the effects of metabotropic glutamate receptor 2/3 manipulation on cognitive performance.

The precise role of mGlu2/3 receptor antagonists on spatial memory deficit following consumption of HFD has not yet been clarified. Therefore, in this study, we examined the effects of post-training administration of mGluR2 and 3 antagonism; LY341495 (Fig.1) on spatial memory in rats fed with high-fat diet by using Morris Water Maze (MWM) task. The MWM task is a relatively simple procedure. The main advantage being the differentiation between the spatial (hidden-platform) and non-spatial (visible platform) conditions. In addition, the MWM testing environment reduces odor trail interference. This has led the task to be used extensively in the study of the neurobiology and neuropharmacology of spatial learning and memory. The MWM plays an important role in the validation of rodent models for neurocognitive disorders such as Alzheimer's disease (15). Because of importance and advantage of MWM task, we used MWM for evaluation of learning and memory deficit in rats fed with high-fat diet.

Results

HFD did not have any effect on memory acquisition.

All animals learned the location of the hidden platform after 4 days of training. Escape latency decreased significantly (control rats: $F(2.786, 19.50) = 12.53$, $P = 0.0001$, HFD group: $F(2.216, 15.51) = 30.60$, $P < 0.0001$, repeated measures one-way ANOVA) after 4 days when compared to the first day (Fig. 3).

Swimming distance also decreased (Fig. 4) but swimming speed did not reveal remarkable change during training ($p > 0.05$, data not shown).

There were not significant differences in Escape latency between experimental groups (Treatment effect: $F(1, 14) = 1.184$, $P = 0.2948$, Day effect; $F(2.693, 37.70) = 36.75$, $P < 0.0001$, Interaction; $F(3, 42) = 1.754$, $P = 0.1706$, two-way ANOVA, Fig. 3). In addition, there no statistically significant differences in swimming distance between experimental groups (Treatment effect: $F(1, 16) = 2.416$, $P = 0.1397$, Day effect; $F(2.938, 47.00) = 33.42$, $P < 0.0001$, Interaction; $F(3, 48) = 1.405$, $P = 0.2528$, Fig. 4).

LY341495 improve HFD-induced reference memory impairment

To assess reference memory at the end of learning, a probe trial was conducted 24 h after the last training trial on day 5. During this test, the platform was removed and time spent in each quadrant of the MWM was recorded. Our results showed that consumption of an HFD leads to spatial memory impairment. There were significant differences in time spent in target zone between experimental groups [$F(3, 20) = 7.031$, $P = 0.0021$, $n = 6-8$, one-way ANOVA, Fig. 5a]. HFD animals spent less time in the target zone in compare with control animals (control rats: $24. \pm 1.36$ sec, $n = 6$ control+LY rats: 24.6 ± 2.5 sec, $n = 6$, HFD rats: 13.7 ± 1.28 sec $n = 8$). Also, LY341495 improved HFD-induced reference memory impairment. HFD animals treated with LY341495 spent more time in the target zone in compare with HFD animals ($P = 0.0449$).

LY341495 and HFD had no effect on swimming speed in the probe test indicating no motor disturbances occurred in the animals (data not shown, $p > 0.05$, one-way ANOVA). In the visible test taken after probe test, all animals could find the platform (Fig. 5b). Escape latencies to find the visible platform during visual discrimination task were the same in all experimental groups ($F(3, 21) = 0.2114$, $P = 0.8874$, one-way ANOVA, Fig. 5b), indicating no visual impairment in the animals.

Discussion

Using a Morris water maze task in rat, the present study showed that HFD did not have any effect on memory acquisition but impaired retrieval of reference memory and induced amnesia. Moreover, HFD induced impairment of memory was restored by pre-test administration of LY341495.

Unlike most previous studies; our results established that spatial learning ability in HFD-treated rats remained intact. Our results show similarity to a study by Zuzanna and colleagues (2), who observed that long-term HFD for 12 months improved the learning ability. They also found that prolonged HFD consumption leads to higher hippocampal volume and higher hippocampal metabolite concentrations, possibly due to increased ketone bodies levels in the blood. Moreover, it has been reported that that increase in humans body mass index is associated with improvement in spatial abilities (16). Also it has been demonstrated that HFD alters gut microbiota but not spatial working memory in early middle-aged Sprague Dawley rats (17). Haleem and Mahmood have reported that HFD improves learning acquisition and memory retention but impair reference memory (18).

Consistent with previous findings, our results verified that HFD induced impairment of memory which was restored by post training administration of LY341495. Cognitive improvement has been observed after treatment with mGluR2/3 antagonists and glutamatergic blockade in some studies (13, 14). mGluR2/3 act as inhibitory autoreceptors in the presynaptic glutamatergic terminals, which inhibit the release of glutamate (19). Therefore, activation of mGluR2/3 reduces glutamate signaling, whereas mGluR2/3 antagonism increases it. High expression of mGlu2/3 receptors have been observed in the hippocampus and amygdala (20, 21). It is known that these brain areas are involved in learning and memory processing, although mixed results have been obtained (22). So, all these regions may be potential sites of LY341495 action.

mGluR2/3 antagonist increase release of glutamate and levels of serotonin in the prefrontal cortex (PFC) (23). It is proposed that increased levels of serotonin may lead to enhanced memory consolidation (24).

Consistent with our results previous studies have reported that mGluR2/3 antagonists improves spatial memory task and acquisition of a visual discrimination (13, 25).

As noted in the introduction section, in our previous work we found that blocking of group II mGluRs increases LTP in rats fed an HFD (4). And it seems that the memory improvement effects of LY341495 are due to its effect on LTP. Underwood and Thompson have found that HFD significantly reduces hippocampal intrinsic excitability in both young adult male and female Long-Evans rats (26), and activation of group II metabotropic glutamate receptors increases the hippocampal network activity (27).

It has been shown that LY341495 administration prevents A β -induced neurodegeneration (28). Also, LY341495 administration into PFC showed a non-significant trend toward increased T-maze test performance in rats (29) and even facilitated performance in working and spatial memory tasks in rats. In addition, post-training administration of LY341495 coupled with administration of 2-methyl 6-(phenylethyl) -pyridine (MPEP) as a mGluR5 antagonist improved MPEP's amnesic effect on recognition memory (30). In contrast, it has been reported that LY341495 administration causes impairment in passive avoidance task and habituation in mice (31, 32) and the LY341495 differentially affected recognition memory in rats (33).

The above studies show the different effects of LY341495 on various cognitive functions. To our knowledge, no studies have addressed the effects of LY341495 on the post-training components of spatial memory in rats fed an HFD. Collectively, our results propose a role for mGluR2/3 antagonists in the handling of memory impairment following consumption of HFD.

Acute administration of LY341495 has been reported to stimulate locomotor activity in mice (34). But in our work, swimming speed was not different among the experimental groups, demonstrating that LY341495 did not affect locomotor activity.

The current work proposes that chronic consumption of an HFD can impair spatial memory and mGluR2/3 inhibition maybe have restored the harmful effects of HFD on memory. We propose that an

HFD may act through mGluRs within the brain to reduce synaptic efficacy and modify synaptic plasticity. Our data suggest that HFD might have a significant effect on cognitive function by promoting neurochemical changes affecting glutamate metabolism.

Conclusion

In conclusion, our results suggested that prolonged consumption of high-fat diet has no effects on the acquisition of spatial learning, but can impair memory retention of the adult male rats and post-training administration of LY341495 can improve HFD-induced reference memory impairment.

Materials And Methods

Ethics Statement

All experimental procedures using rats were conducted in accordance with the animal care and use guidelines approved by the institutional ethics committee at Hamadan University of Medical Sciences and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All efforts were made to minimize suffering. The operations that could cause pain and distress were performed in another room in the absence of other animals.

Animals, LY341495 administration and experimental design

Twenty-four adult male Wistar rats weighing 250–300 g obtained from Pasteur Institute of Tehran, Iran. The animals were housed in an air-conditioned room at $22 \pm 2^\circ\text{C}$ with a 12-h light/dark cycle. The animals were kept in cages with 2–3 rats in each cage. Standard animal chow and water were freely available. After one week of adaptation, subjects were randomly divided into following groups (N = 6–8): control group consumed an ordinary diet; HFD group received high-fat diet only; control+LY group: control animals treated with LY341495; HFD+LY group: HFD animals treated with LY341495. Animals were maintained on standard diet or HFD regimes as per the protocol for 10 weeks before subjecting them for testing using Morris water maze (MWM). After 10 weeks, MWM task was used to evaluate the spatial learning and memory in rats. We dissolved the selective and highly potent antagonist for mGluR2/3, (2S)-2-amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid (LY341495, Tocris) in $\sim 10 \mu\text{L}$ of 0.1 M NaOH and brought to dose volume using 0.9% sterile saline solution. A single intraperitoneal injection (i.p) of LY341495 (3 mg/kg) as an antagonist of mGluR2/3 was done 30 minutes before retention test (31, 35). At the end of behavioral test, the animals were euthanized under urethane anesthesia (1.8 g/kg; i.p.) and decapitated. Experimental design and schedule of MWM task are shown in Fig. 2.

Diet composition

Rats were fed with standard rat food pellets for 7 days in order to recover from transportation. The HFD was designed according to the standard HFD D12492 Dietary, which is used for develop obesity (36). Firstly, Pellet dry powder was mixed slowly for 15 min using an electric mixer. Subsequently, animal fatty oils (8.3%), hydrogenated oil (4.05%), cholesterol (1%), and sugar (17/3%) were added to the mixture of powder and were mixed for 15 min. An HFD has a caloric density of approximately 5.24 kcal/g. A standard laboratory rodent chow diet (Lab Diet) was used for the control diet. This control diet has a caloric density of approximately 3.0 kcal/g.

Morris water maze (MWM) task

Apparatus

MWM task is a hippocampal-dependent test of spatial learning for rodents (37, 38). The water maze apparatus consisted of a black-painted circular pool, (155 cm diameter, 60 cm height), filled to a depth of 35 cm with water ($22 \pm 1^\circ\text{C}$). The pool was divided into four equal quadrants. A hidden platform (10 cm in diameter), made of Plexiglas, was located 2 cm under the water surface in the center of the eastern quadrant (target quadrant). A video-computer tracking system (CCD camera, Panasonic Inc., Japan) was used to record the rats' swim path for later analysis (EthoVision software XT7, Netherland). Large posters on the wall of the room served as visual cues.

Habituation

Twenty-four hours before starting the hidden platform training, rats were given a 60 s swim in the tank without platform for adaptation to the environment.

Hidden Platform Training

The training session was done according to the previous procedure conducted in our laboratory (37, 39, 40). In summary, training session was consisted of one block of 4 trails per day for four consecutive days. Each trial was started by placing the animal in one of the four quadrants. Animals were allowed to swim the in pool during a period of 90 s to find the hidden platform that was kept in the middle of one of the four quadrants. If an animal did not find the platform within this period, it was manually guided to the platform by the investigator. The rats rested 10 min between the two consecutive trials. The escape latency (i.e., time to reach the platform) and swimming distance were used to assess acquisition of the water maze task. Swimming speed was used to assess the motor activity of the rats. Twenty-four hours after the 4th session the spatial probe test was given. In the spatial probe test, the platform was removed, and rats were allowed to swim for 60 s before they were removed. Animals were released in the water in a location that was exactly opposite from where the platform was placed. Behavior was recorded with a video tracking system. Escape latencies and swim speeds were recorded for subsequent analysis.

Visual test

Thirty minutes after the probe trial, the platform was elevated above the water surface; covered by bright color aluminum foil, and placed in a different zone and rats were allowed to swim and find the visible platform during 60 s in order to test their visual ability. All experiments were conducted between 10:00 and 12:00.

Statistical analysis

Data were presented as mean \pm SEM and processed by commercially available software GraphPad Prism[®] 8.0.2. In the behavioral study (MWM), the data of the training trials were analyzed using a two-way analysis of variance (ANOVA) with days as repeated measures factor and treatments as between subjects' factor. For statistical analyses of probe and visibility trial data, one-way ANOVA was used. Two-way and one-way ANOVA were followed by post hoc analysis (Bonferoni and Tukey's tests, respectively). The level $P < 0.05$ was considered as statistically significant.

Abbreviations

HFD: High-fat diet

CNS: Central nervous system

iGluRs: ionotropic glutamate receptors

mGluRs: Metabotropic glutamate receptors

NMDA: N-methyl-D-aspartate

AMPA: amino-3-hydroxy-5-methyl-4-isoxazolepropionate

DG: dentate gyrus

LTP: Long-term potentiation

MWM: Morris Water Maze

PFC: Prefrontal cortex

MPEP: 2-methyl-6-(phenylethynyl)-pyridine

LY341495: (2S)-2-amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid

Declarations

Authors' contributions

SAK designed the project, wrote the manuscript and performed the statistical analysis, revised the manuscript and supervised the project. HM, EH, IS and HS were involved in laboratory works and experimental design of the work. AS, AK and JK were involved in data collection and lab assessments, and study designing. All authors read and approved the final

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data are available for any scientific use with kind permission.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All experimental procedures using rats were conducted in accordance with the animal care and use guidelines approved by the institutional ethics committee at Hamadan University of Medical Sciences (Code of Ethics Committee: IR.UMSHA.REC.1398.323) and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

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Figures

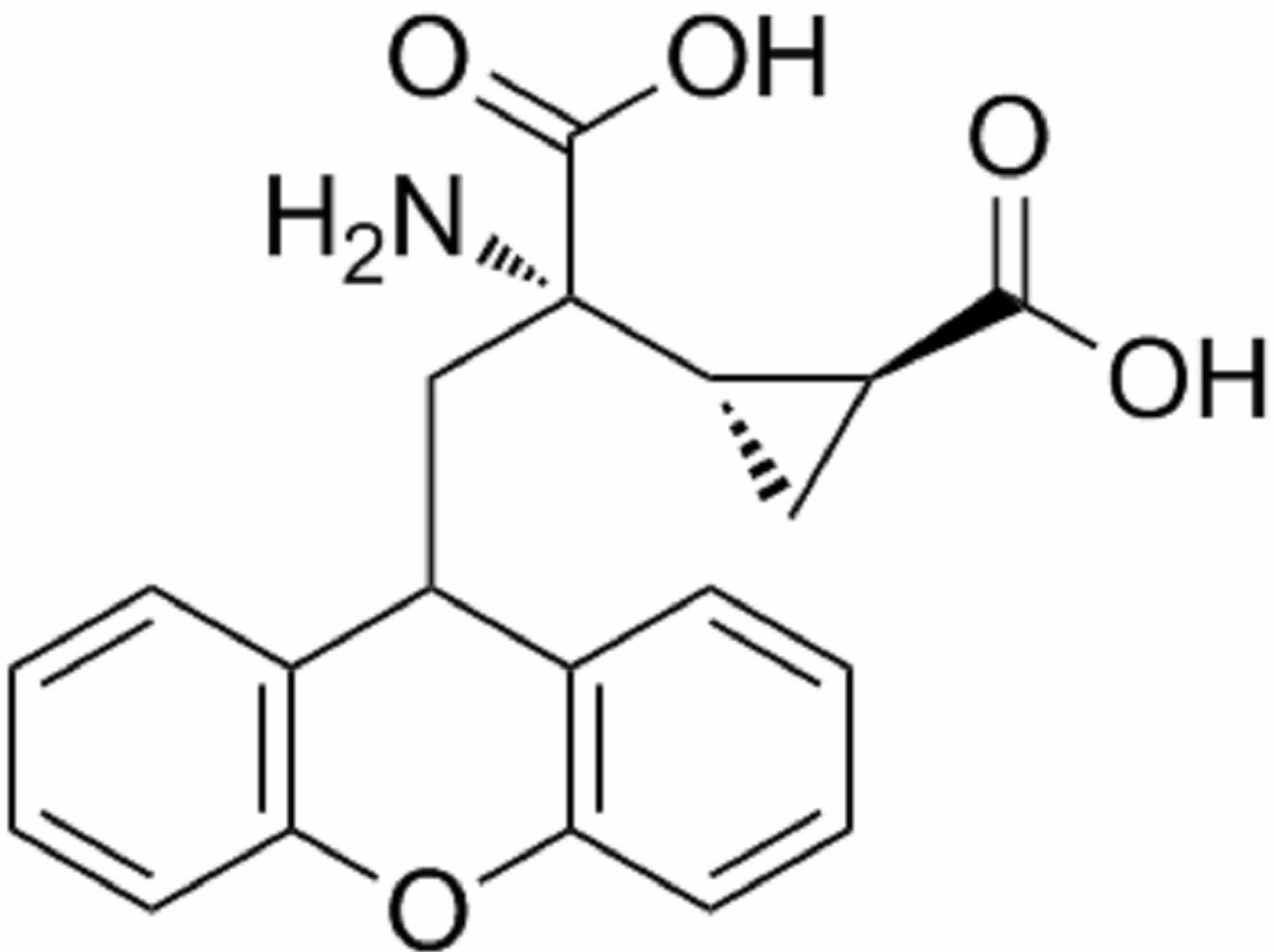


Figure 1

LY341495 Chemical structure. Potent and selective group II metabotropic glutamate receptors (mGluR2/3) antagonist.

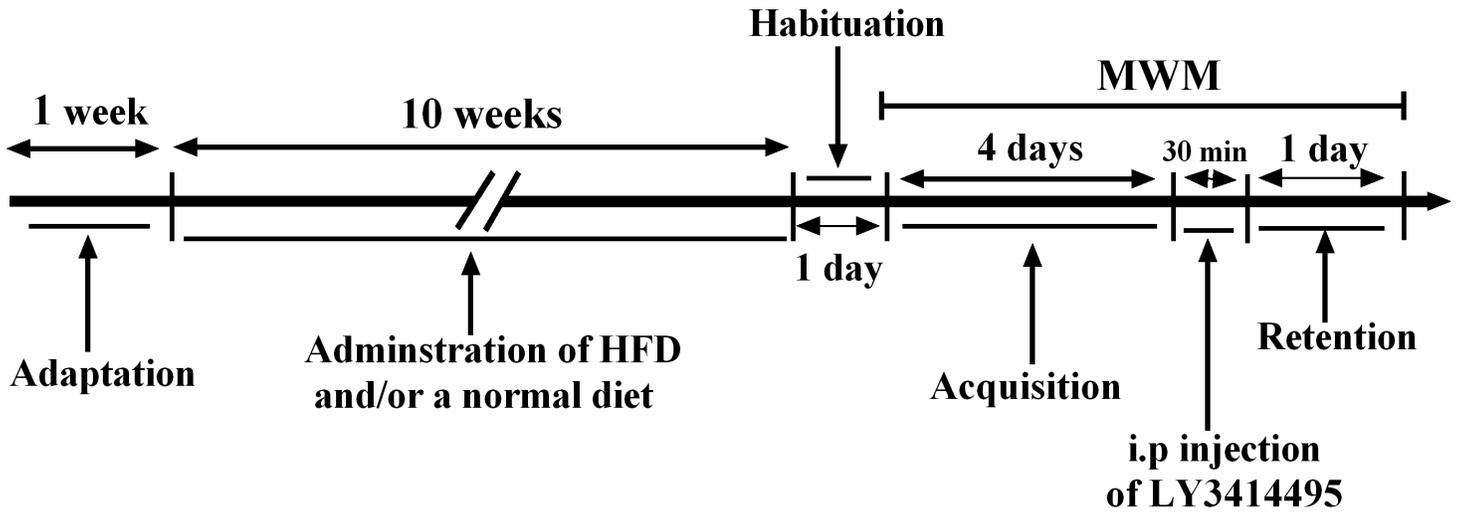


Figure 2

Experimental design and schedule of behavioral tests. After one week of adaptation, animals were maintained on standard diet or HFD regimes as per the protocol for 10 weeks before subjecting them for testing using Morris water maze (MWM). After 10 weeks, MWM task was used to evaluate the spatial learning and memory in rats. i.p injection of LY3414495 as an antagonist of mGluR2/3 was done 30 minutes before retention test.

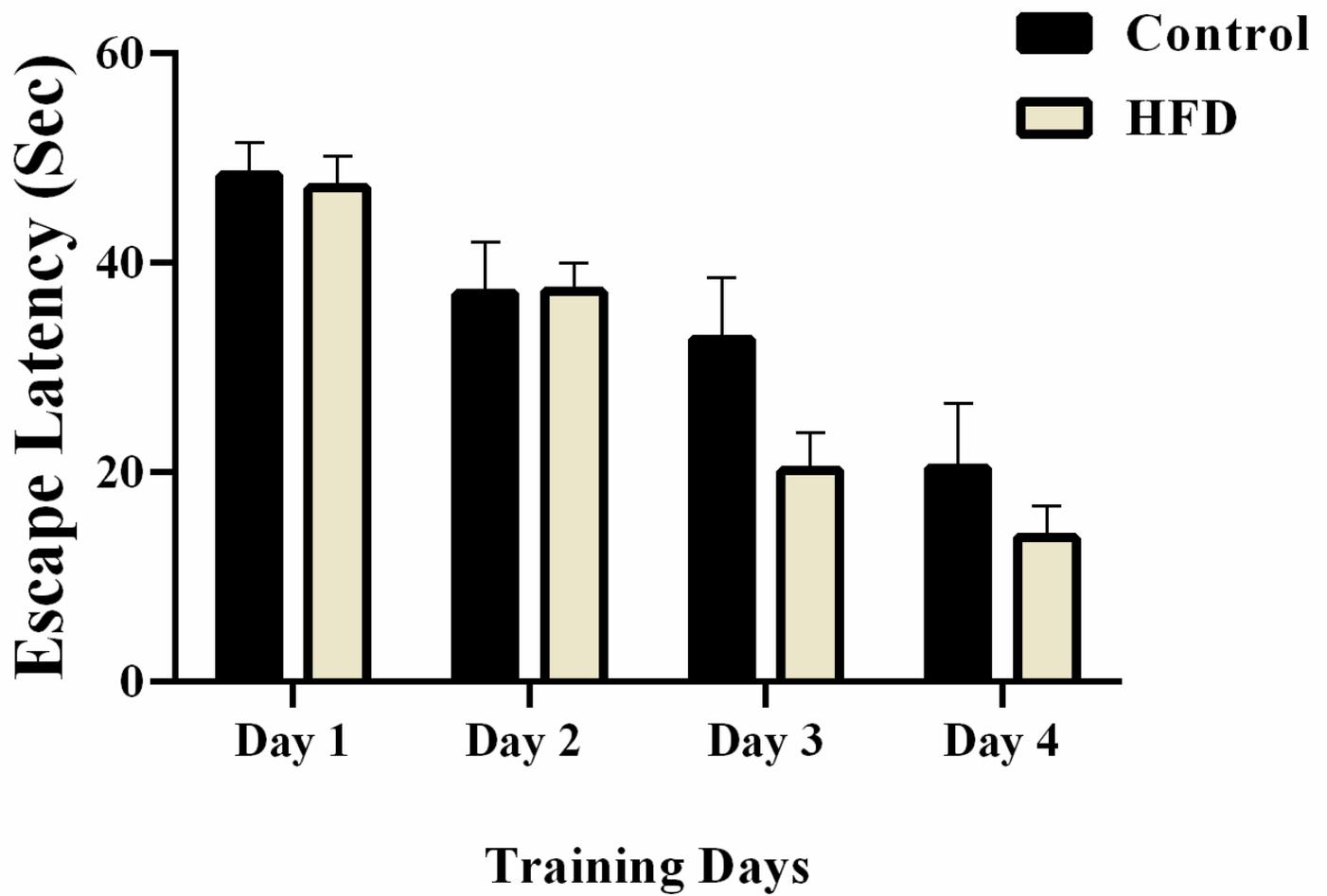


Figure 3

Effects of high-fat diet on escape latency in the training days of water maze task. Data presented as means \pm S.E.M.

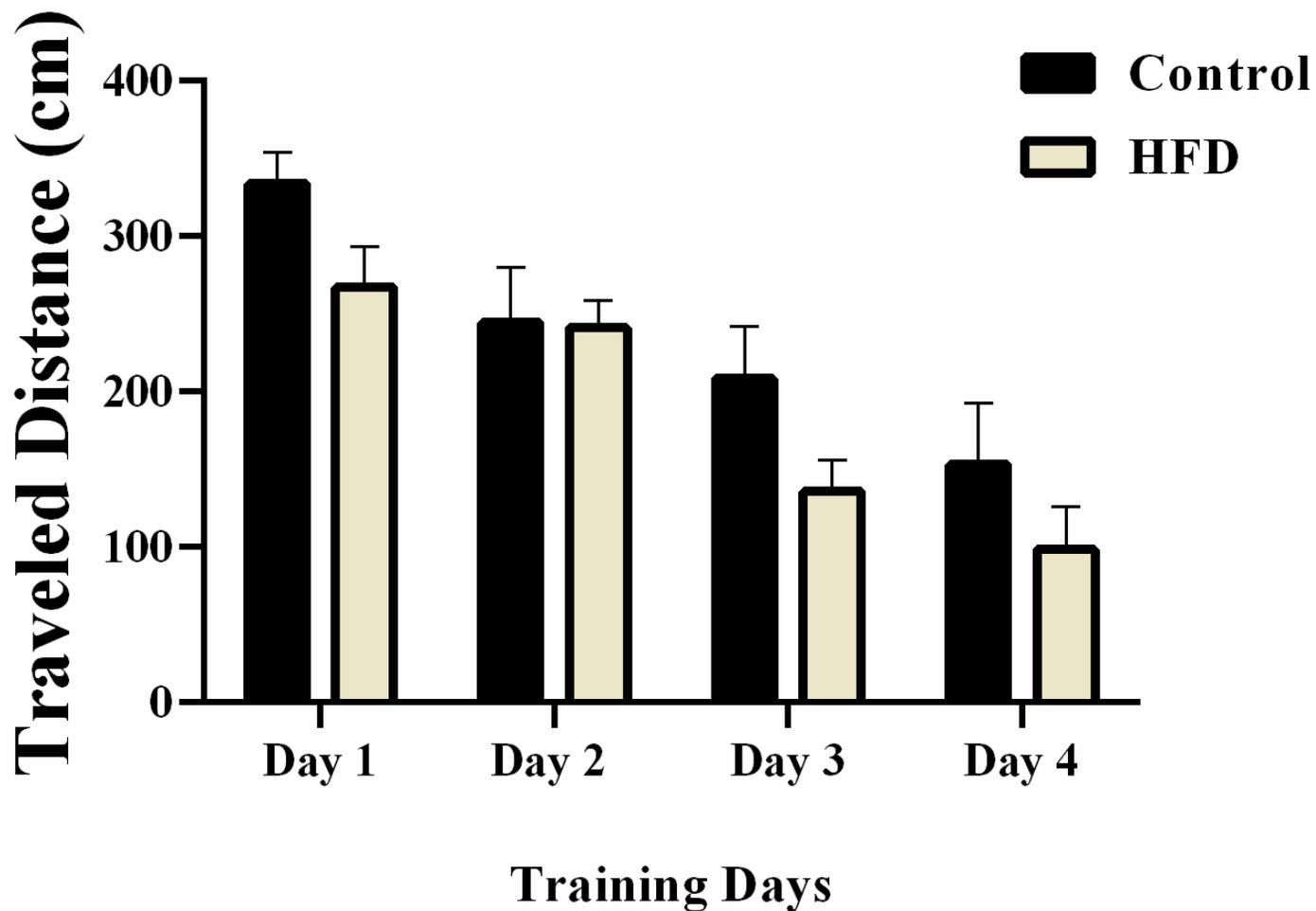


Figure 4

Effects of high-fat diet on traveled distance in the training days of water maze task. Data presented as means \pm S.E.M.

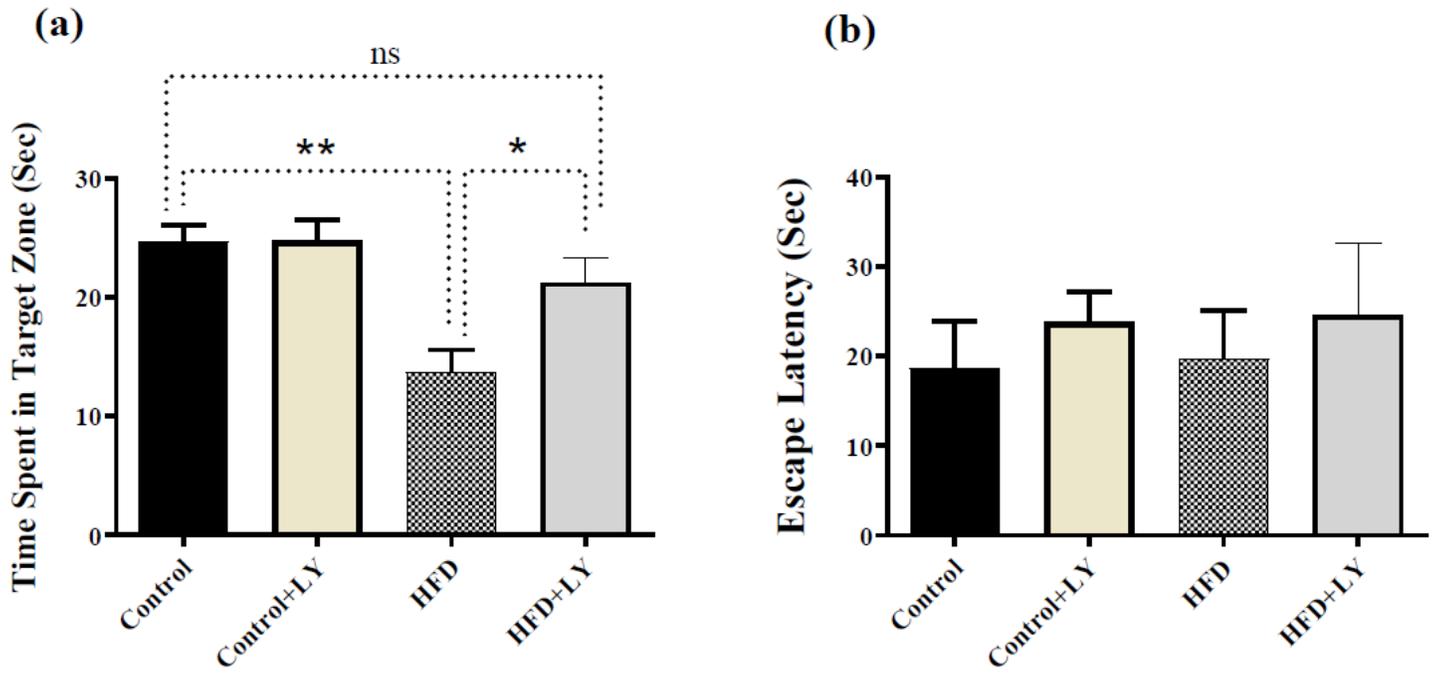


Figure 5

Spatial reference memory was measured in a probe test. Animals fed with a high fat diet spent less time in the target zone (a). HFD animals treated with LY341495 spent more time in the target zone in compare with HFD animals. Animals in all groups showed no difference in escape latency (b) to find a visible platform. Data presented as means \pm S.E.M. * $p < 0.05$, ** $p < 0.01$, ns; not significant.

Supplementary Files

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- [NC3RsARRIVEGuidelinesChecklistfillable.pdf](#)