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The effect of ghrelin and adenosine mono phosphate kinase (AMPK) on the passive avoidance memory in male wistar rats

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1. Introduction

Learning is the biological process of acquiring new knowledge about the world, and memory is the process of retaining and reconstructing that knowledge over time. Most of our knowledge of the world and most of our skills are not innate but learned. (Kandel, Dudai et al. 2014). The hippocampus plays an essential role in the process of learning, memory and emotional Responses (Kim et al., 2017).

Ghrelin is a unique 28-amino acid peptide hormone mainly produced in the stomach. Ghrelin exists in two major molecular forms, acylated ghrelin (AG) and unacylated ghrelin. The acylated form of ghrelin exerts its effects through the activation of the growth hormone (GH) secretagogue receptor 1a (GHS-R1a) to release GH (Chung, Seo et al. 2008).The hypothalamus represents the most important endogenous source of the ghrelin in the central nervous system (CNS) (Ferrini, Salio et al. 2009). The acylated peptide ghrelin is released from the gut during fasting or starvation and is carried to the hypothalamus, where it acts as a “hunger signal” to increase appetite (Hardie and Ashford, 2014). Ghrelin has much broader physiological functions as an orexigen, including stimulation of growth hormone (GH) secretion, gastrointestinal motility and cardiac contraction, inhibition of energy metabolism and insulin secretion and inhibition of inflammation and apoptosis (Fujitsuka et al., 2016). Ghrelin caused an anxiolytic-like effect in both the open field and elevated plus maze tests (Jensen et al., 2016). Qi et al. have shown that overproduction of ghrelin in the hypothalamus leads to a temporary increase in food intake up to 3 weeks associated with increases in bodyweight (Qi et al., 2015).

Ghrelin activates AMPK in the hypothalamus (Hardie and Ashford, 2014). AMPK is a transcriptional regulator that has emerged as a major energy sensor that maintains cellular energy homeostasis (Han et al., 2016). Ghrelin activates the G-protein-coupled receptor GHSR1, triggering production of IP_3 and consequent release of intracellular Ca^{2+} in the presynaptic neuron. The released Ca^{2+} then triggers phosphorylation of AMPK via CaMKKβ. AMPK is proposed to activate ryanodine receptors (RyR) that also trigger Ca^{2+} release, setting up a positive feedback loop that allows continued Ca^{2+}-dependent release of the neurotransmitter glutamate onto the NPY/ AgRP neurons even after ghrelin release has stopped (Yang et al., 2011). AMPK activity in the CA1 negatively regulates contextual fear memory formation and structural plasticity through mTORC1 signaling. Compound c is AMPK inhibitor. (Han et al., 2016).

There are discrepancy reports about ghrelin effect on memory; Many previous studies have shown that ghrelin enhances memory processes, for example injections of ghrelin into the hippocampus, amygdala or dorsal raphe nucleus dose-dependently increased memory retention in the step-down passive avoidance task (Carlini et al., 2004).

Toth et al. showed that post-training intraamygdaloid injection of acylated-ghrelin improved memory consolidation in the step-through passive avoidance test, but injection of D-Lys-3-GHRP-6 alone, was ineffective (Tóth et al., 2009). In contrast to memory enhancement, impairments induced by ghrelin administration have been reported in neonatal chicks (Carvajal et al., 2009). Also intra-CA1 (intra-LA) infusion of ghrelin blocks the acquisition of hippocampus-dependent spatial memory (Wang, 2016). GHS-R1a knockout mice exhibited clearly better performance in Morris water maze, suggesting that GHS-R1a activation actually interferes with acquisition of spatial memory (Albarran-Zeckler et al., 2012).

Considering the above mentioned reports, the aim of this study was to further clarify the effect of ghrelin on memory acquisition and retention. The AMPK dependency of this effect was also examined.

2. Materials and methods

2.1. Drugs

Ghrelin was purchased from Sigma (USA). Dorsomorphin (Compound C) was purchased from Cayman chemical (USA). Ketamine and xylazine were purchased from Alfasan (Netherland). Ghrelin (3 nmol) (Carlini et al., 2010) and different doses (0.1, 1, 10 μg/rat) of compound C were dissolved in normal saline to get a final intended

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concentration, immediately before use. Then we selected the effective dose of compound C (10 μg/rat) based on the dose-response test.

2.2. Animals

In total, 64 male wistar rats weighing 200–250 g were randomly distributed into 8 groups of 8 each. Rats were obtained from the breeding colony of Department of Physiology, Guilan University of medical sciences. Animals were housed four per cage in a temperature (24 ± 2 °C) controlled room that was maintained on a 12:12 light cycle (light on at 07:00 a.m.). Following surgery, rats were housed individually and had free access to food and water in their home cage. All animal experiments were carried out in accordance with the national institute of health guide for the care and use of laboratory animals' publication no. 8023 revised 1978. All protocols were also approved by Ethical Committee of Guilan University of Medicale Sciences (code NO. IR.GUMS.REC.1369.255).

2.3. Surgical procedures

Experimental animals were prepared with guide cannula implantation (23 gauge needle) at least 7 days before their use. The rats were anesthetized with intraperitoneal (i.p.) injection of Ketamine (100 mg/kg) and xylazine (10 mg/kg) and the cannulae were stereotaxically (Stoelting, stereotaxic apparatus, USA) bilaterally implanted 1 mm above the CA1. The necessary coordinationwas made based on Paxinos and Watson atlas (Paxinos and Watson, 2007)such as AP: − 3/8 mm caudal to bregma, Lat: ± 2/2 mm, DV: − 2/7 mm vertical from the skull surface (the guide cannulae were 1 mm above the appropriate injection place). The guide cannulae were secured in place using two stainless steel screws anchored to the skull with dental acrylic cement. They were sealed with occluding stylette in the recovery period (7 days).

2.4. Microinjection procedure

Intra-hippocampal injections3nmol (Ghrelin and Compound C) were carried out via guide cannula with injection needles (27-gauge) that were connected by polyethylene tubing (PE20, Stoelting) to a 5 μl Hamilton micro syringe. The infusion volume for all of the drugs was 1 μl and it was delivered over a 1 min period. The injection needle (extending 1 mm from the end of the guide cannula) was left in place an additional minute before it was slowly withdrawn.

2.5. Passive avoidance task

Each rat was placed in the white start chamber of the passive avoidance apparatus facing the sliding door. After 10 s the door was raised to let the animal enter the second, black chamber. When the animal stepped into the black chamber with all four paws, the door was closed and the rat remained there for 20 s. Then the animal was removed to be placed in a temporary cage. Thirty min later, the rats were again placed in the white start chamber for 10s, then the door was raised to let the animal enter the black chamber and the door was closed, but this time an electrical shock of 1 mA and 50 Hz lasting for 2 s was delivered. After 20 s, the rat was placed into the temporary cage. 2 min later, the same testing procedure was repeated. The rat had a foot shock each time it stepped into the black chamber with all four paws. When the rat remained in the white compartment for a 2 min time period, the training was terminated. All the animals learned the task with 2 maximum trials. On the second day, a retrieval test was done to evaluate long-term memory. Each animal was placed in the white start chamber for 10 s, then the door was raised and the step-through latency (STL), the time spent in the dark compartment (TDC) up to 300 s was measured.

2.6. Experimental design

The researchers performed two sets of studies as follows:

In the first series of experiments saline, ghrelin 3 nmol, compound C (0.1, 1, 10 μg/rat) + ghrelin 3 nmol were injected before the training session

Ghrelin 3 nmol and compound C10 μg/rat were injected 15 min and 25 min before the training session, respectively.

In the second set of experiments, saline, ghrelin 3 nmol, compound C10 μg/rat + ghrelin 3 nmol were injected before the retrieval test session

Ghrelin 3 nmol and Compound C10 μg/rat were injected 15 min and 25 min before the retrieval test session, respectively.

2.7. Statistical analysis

The data are presented as means ± S.E.M. One-way analysis of variance (ANOVA) was performed with Tukey multiple comparisons post-hoc posttest using Statistical Package for the Social Sciences (SPSS) version 19 for Windows 7 (IBM software, USA). In all experiments, $P < 0.05$ was considered statistically significant.

2.8. Verification of cannula placements after completion of the experiments

For this purpose, 1 μl of methylene blue 2% dye was injected into CA1 region of rats and then each animal was euthanized with an overdose of ether. The brains were removed and fixed in a 10% formalin solution 5 days before sectioning. Sections were examined to determine the location of the cannulas aimed for CA1 region of hippocampus. The cannula placements were verified using the atlas of Paxinos and Watson (Fig. 1).

3. Results

3.1. The effect of pre-training intra-hippocampal injection of saline, ghrelin 3 nmol, compound C (0.1, 1, 10 μg/rat) + ghrelin 3 nmol on the passive avoidance task

The results showed that there was no significant difference between the control and ghrelin 3 nm groups in STL and TDC criteria at 24 h, 48 h and 10 days after training, as shown in fig. 2.

Data analysis indicated that there was no significant difference among the ghrelin 3 nmol and Compound C (0.1,1 μg/rat) + ghrelin 3 nmol groups in STL and TDC criteria at24h, 48 h and 10 day after training (Fig. 3 and 4).

Compound C 10 μg/rat + ghrelin 3 nmol showed a tendency towards increased STL (Fig. 5), however, failed to reach statistical significance compared to ghrelin 3 nmol group at 24 and 48 h after training. Compound C10 μg/rat + ghrelin 3 nmol significantly

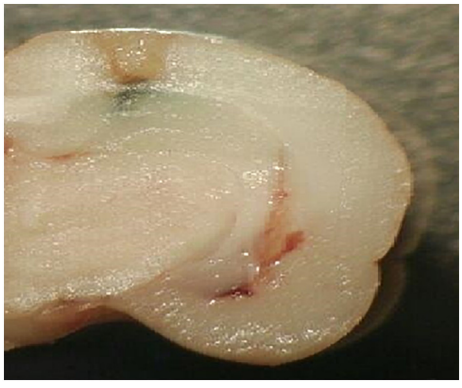

Fig. 1. Representative the position of CA1and the tip of the implanted cannula.

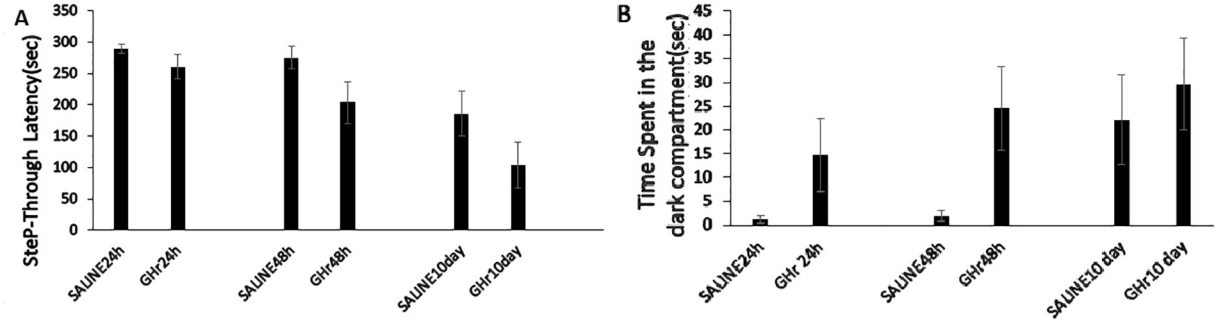

Fig. 2. The effect of pre-training intra-hippocampal injection of saline and ghrelin 3 nmol on the passive avoidance task.
(A) The latency of entering the dark compartment or step-through latency (STL). (B)The time spent in the dark compartment (TDC). (24, 48 h and 10 days after training). Data are expressed as mean + SEM, $n = 8$ for each group.

increased STL as compared to ghrelin 3 nmol group at 10 days ($P < .05$) after training. Compound C (10 μg/rat) + ghrelin 3 nmol showed a tendency towards decreased TDC, however, failed to reach statistical significance compared to ghrelin 3 nmol group at24h, 48 h and 10 day after training.

Fig 5. The effect of pre-training intra-hippocampal injection of ghrelin 3nmol and Compound C (10μg/rat) + ghrelin 3nmol on the passive avoidance task.

(A) The latency of entering the dark compartment or step-through latency (STL). (B) The time spent in the dark compartment (TDC). (24, 48h and 10 days after training). Data are expressed as mean + SEM, n = 8 for each group. (*P < 0.05).

3.2. The effect of pre-test Intra-hippocampal injection of saline, ghrelin 3 nmol, compound C 10 μg/rat + ghrelin 3 nmol, on the passive avoidance task

As indicated in Fig. 6, the result showed that there was significant difference between the control and ghrelin 3 nmol groups in STL criteria at 24 h ($p < .001$) after training session. Pre-test injection of ghrelin 3 nmol showed a tendency towards decreased STL, however, failed to reach statistical significance compared to saline group at 48 h and 10 days after training session. Pre-test injection of ghrelin3nmol showed a tendency towards increased TDC, however, failed to reach statistical significance compared to saline group at24h, 48 h and 10 days after training session.

The data indicated there was no significant difference between animals that received ghrelin 3 nmol and those that received Compound C 10 μg/rat + ghrelin 3 nmol in STL and TDC criteria at 24 h,48 h and 10 days after training session (Fig. 7).

4. Discussion

In the present study, we investigated the effect of ghrelin and AMPK on passive avoidance memory.

Our results indicated that pre-training intra-hippocampal injection of ghrelin 3 nmol had no effect on memory retrieval, but Pre-test intra-hippocampal injection of ghrelin 3 nmol significantly decreased STL at 24 h after training. Many previous studies have shown that ghrelin enhances memory processes; for example, Carlini et al. by using a Step-down passive avoidance task reported that pre-training intrahippocampal injections of the ghrelin improved long-term memory without altering the short-term, but when the ghrelin was injected pre-test, no changes were seen in the memory performance. Also, post-training injections of the peptide increased both short and long-term memory. They concluded that ghrelin when injected into the hippocampus could affect either the memory acquisition or consolidation but certainly did not affect the retrieval (Carlini et al., 2010). On the other hand, they showed in a separate study that ghrelin when injected i.c.v. increases the memory retention in the step-down paradigm in a dose-dependent manner(Carlini et al., 2002). Intrahippocampal injection of ghrelin at the dose of 3 nmol significantly improved spatial memory in PTZ + ghrelin group compared to PTZ group. These findings suggest that ghrelin as a neuropeptide can improve spatial memory in PTZ-treated rats (Babri et al., 2013). Beheshti et al. showed that blocking the GHS-R1a in the rat brain by means of a selective antagonist impairs memory encoding and supports the idea that the endogenous ghrelin signaling in the rat brain is crucial for memory acquisition and consolidation (Beheshti and Shahrokhi, 2015). In contrast to memory enhancement, memory impairments induced by ghrelin have been reported; for example, Zhao et al. found that systemic ghrelin treatment stimulated neurogenesis in the adult hippocampus, but had no effect on spatial memory formation. Consistently, it did not affect the

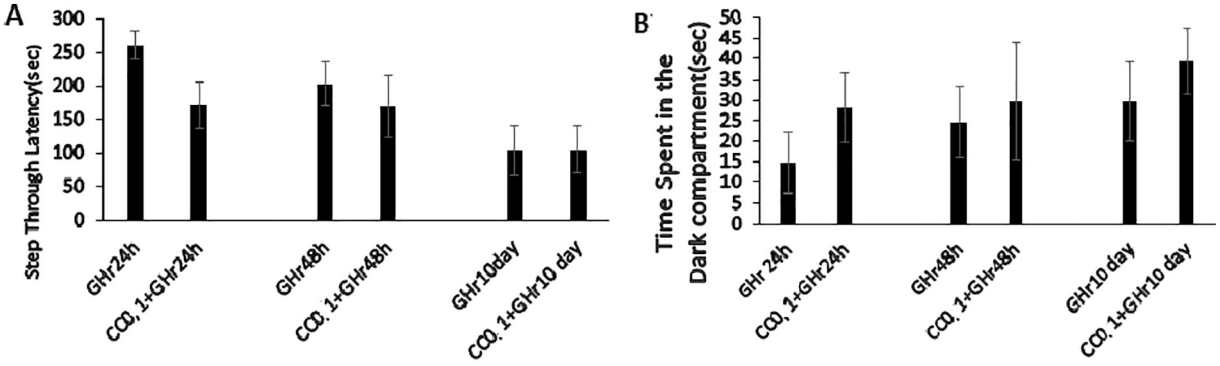

Fig. 3. The effect of pre-training intra-hippocampal injection of ghrelin 3 nmol and Compound C (0.1 μg/rat) + ghrelin 3 nmol on the passive avoidance task.
(A) The latency of entering the dark compartment or step-through latency (STL).
(B) The time spent in the dark compartment (TDC). (24, 48 h and 10 days after training). Data are expressed as mean + SEM, $n = 8$ for each group.

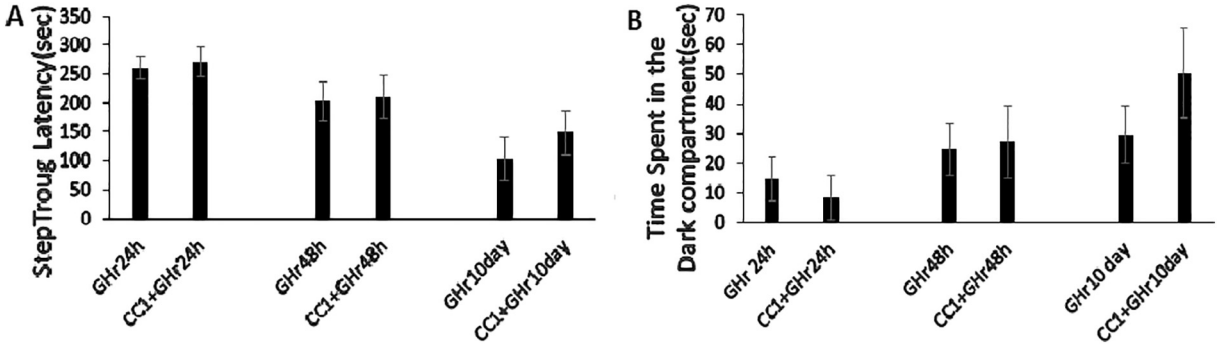

Fig. 4. The effect of pre-training intra-hippocampal injection of ghrelin 3 nmol and Compound C (1 μg/rat) + ghrelin 3 nmol on the passive avoidance task.
(A) The latency of entering the dark compartment or step-through latency (STL).
(B) The time spent in the dark compartment (TDC). (24, 48 h and 10 days after training). Data are expressed as mean + SEM, n = 8 for each group.

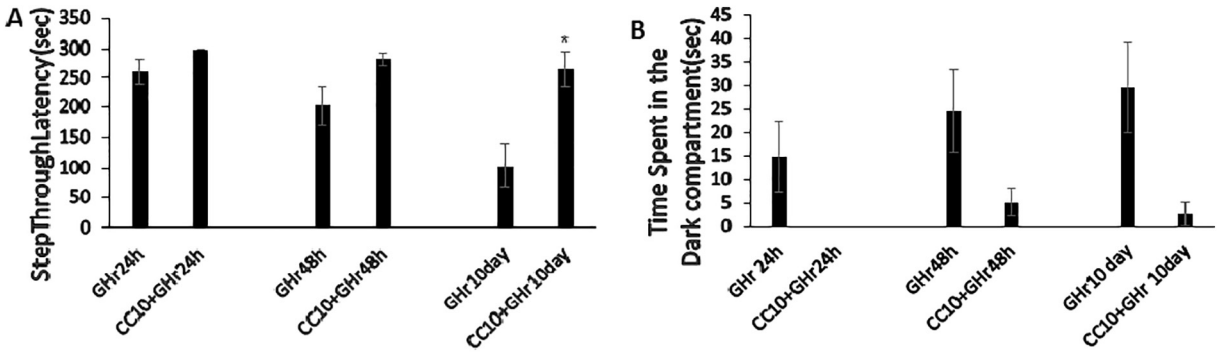

Fig. 5. The effect of pre-training intra-hippocampal injection of ghrelin 3 nmol and Compound C (10 μg/rat) + ghrelin 3 nmol on the passive avoidance task. (*$P < .05$).
(A) The latency of entering the dark compartment or step-through latency (STL).
(B) The time spent in the dark compartment (TDC). (24, 48 h and 10 days after training). Data are expressed as mean + SEM, n = 8 for each group.

incorporation of newborn neurons into the spatial memory circuits. On the contrary, local infusion of ghrelin impaired spatial memory formation, but did not affect adult neurogenesis. (Zhao et al., 2014). A human study demonstrated that ghrelin impaired procedural memory consolidation (Dresler, 2010), and another population study showed that serum ghrelin levels were negatively correlated with declarative memory in elderly adults (Spitznagel, 2010).

In the hippocampus, ghrelin stimulated CREB signaling by ghrelin receptor and cAMP/PKA signaling pathway and the cAMP-dependent amplification of PKA resulted in the enhancement of NMDA receptor function by increasing the number of phosphorylated NR1subunits (Cuellar and Isokawa, 2011). Ghrelin activates AMPK in the hypothalamus and the G-protein-coupled receptor GHSR1, triggering production of IP_3 and consequent release of intracellular Ca^{2+}in the presynaptic neuron. The released Ca^{2+} then triggers phosphorylation of AMPK via CaMKKβ. AMPK is proposed to activate ryanodine receptors (RyR) that also trigger Ca^{2+} release, setting up a positive feedback loop (AMPK → RyR → Ca^{2+} → CaMKK → AMPK) that allows continued Ca^{2+}-dependent release of the neurotransmitter glutamate onto the NPY/AgRP neurons even after ghrelin release has stopped (Yang et al., 2011). AMPK activity in the CA1 negatively regulates contextual fear memory formation and structural plasticity through mTORC1 signaling (Han et al., 2016).

In this study, we found that pre-training injection of compound C (10 μg/rat + ghrelin3 nmol) contrasted with the reduced ghrelin effect on memory.Due to antagonistic effect of compound C on AMPK, it seems to be part of the probable reductive effect of ghrelin on memory through the AMPK path.

Some of the studies are in accordance to our findings. Ditachio and his collegues have reported that the activation of AMPK increase

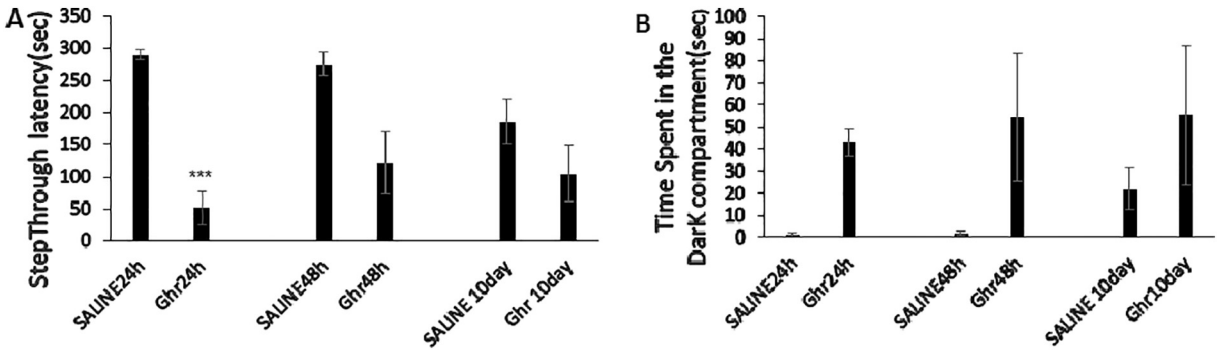

Fig. 6. The effect of pre-test intra-hippocampal injection of saline and ghrelin 3 nmol on the passive avoidance task.
(B) The time spent in the dark compartment (TDC). (24, 48 h and 10 days after training). Data are expressed as mean + SEM, n = 8 for each group. (***$p < .001$)

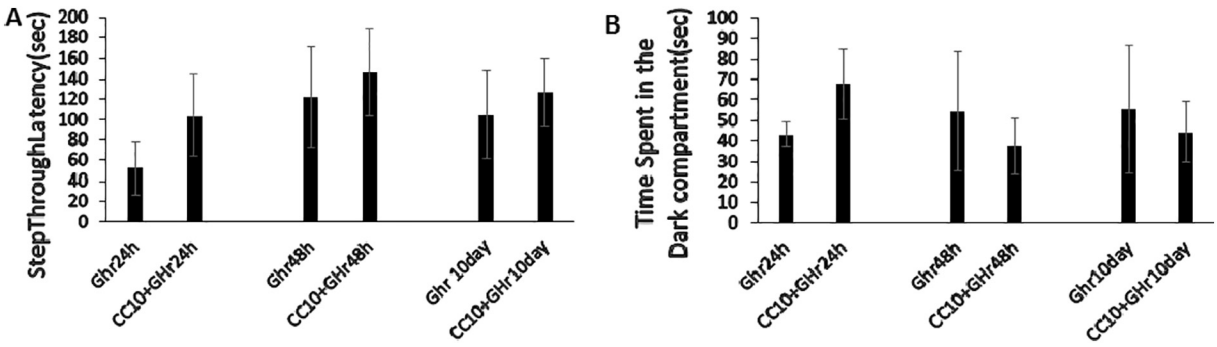

Fig. 7. The effect of pre-test intra-hippocampal injection of ghrelin 3 nmol and Compound C (10 μg/rat) + ghrelin 3 nmol on the passive avoidance task.
(A) The latency of entering the dark compartment or step-through latency (STL).
(B) The time spent in the dark compartment (TDC). (24, 48 h and 10 days after training). Data are expressed as mean + SEM, n = 8 for each group.

memory dysfunction in male AβPP (amyloid precursor protein) mice (Ditacchio et al., 2015). Also, it was reported that the activation of AMPK impaired long-term spatial memory (Green et al., 2011). On the other hand, one study is in consistence to our findings. It was showed that systematic administration of the AMPK agonist AICAR increased spatial memory and improved motor function in young and old female mice (Kobilo et al., 2011; Kobilo et al., 2014). This inconsistency may be attributable to the specific animal models used, species, gender, or route of administration (Han et al., 2016).

Studying other possible signaling pathway of ghrelin such as protein kinase C (PKC) and phosphatidyl inositol 3 –kinase (PI3K) could further elucidate the link between ghrelin and memory. The lack of molecular experiments were one of the main limitations of this study.

5. Conclusion

Although the application of ghrelin did not affect the acquisition phase of memory, it could attenuate the passive avoidance memory retention after 24 h. As the co- administration of ghrelin and compound C improved the reductive effect of ghrelin on memory, it could be concluded that this effect is at least in part, mediated by AMPK pathway.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this work.

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