

Acute and chronic zolpidem administration changes hippocampal long-term potentiation (LTP) as a possible mechanism of memory impairment

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ABSTRACT

Objective(s): Zolpidem is a non-benzodiazepine GABAA receptor positive modulator commonly used to treat short-term insomnia. Given its widespread use, understanding its potential impact on cognitive function and synaptic mechanisms is of great interest. This study aimed to investigate the effects of acute and chronic zolpidem administration on hippocampal long-term potentiation (LTP) as a possible mechanism underlying memory impairment in rats.

Materials and Methods: Three groups of rats were used in this study: control, acute (received a single dose of zolpidem, 15 mg/kg), and chronic (received daily doses of zolpidem, 15 mg/kg, for 30 consecutive days). Spatial learning and memory were assessed using the Morris water maze. Basic synaptic transmission and LTP were assessed by recording field excitatory postsynaptic potentials in the hippocampus.

Results: No significant differences were observed in spatial learning among the groups. However, evaluation of spatial memory showed that acute and chronic treatment significantly impaired memory performance compared to the control group. Spatial memory was more severely impaired in the chronic group than in the acute group. Electrophysiological data showed that although LTP was induced in both acute and chronic treatment groups, both had significantly lower LTP magnitude than the control group.

Conclusion: Chronic zolpidem administration caused significantly greater impairment of spatial memory than acute administration, whereas LTP induction was similarly reduced in both groups. These findings suggest that long-term zolpidem use may pose a greater risk to cognitive function than acute exposure.

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Introduction

Zolpidem is an imidazopyridine derivative (1) and a non-benzodiazepine hypnotic agent commonly prescribed for the short-term treatment of insomnia (2). It acts as a positive allosteric modulator of γ -aminobutyric acid type A (GABAA) receptors, with high affinity and efficacy for $\alpha 1$ subunit-containing receptors ($\alpha 1$ -GABAARs) (3). As GABA is the principal inhibitory neurotransmitter in the central nervous system (4), modulation of GABAA receptors has been strongly associated with cognitive performance, particularly learning and memory (5). Agonists of GABAA receptors are well documented to impair memory function, whereas antagonists can facilitate memory consolidation (6). For example, antagonists such as bicuculline (7) and flumazenil (8) enhance memory performance, while agonists including muscimol (9) and diazepam (10) disrupt memory formation (11).

Although zolpidem, as a positive modulator of GABAA

receptors, has been shown to induce amnesic effects (12), its cognitive consequences remain controversial (13). Some studies indicate that zolpidem impairs spatial or working memory in animals (3) or humans (14), while others report no significant cognitive deficits (15). Conversely, some clinical observations suggest potential improvements in specific cognitive domains under certain conditions (16, 17). For instance, Verster *et al.* reported dose-dependent impairment in word recall and recognition several hours after zolpidem administration in healthy volunteers (18). In contrast, Gunja *et al.* highlighted potential risks associated with long-term use, particularly in older adults (19). Additionally, Masato Higashima *et al.* showed that LTP induction was unaffected at 1 μ M zolpidem but was reduced at 10 μ M, likely due to its lower affinity for $\alpha 2$ -containing GABAA receptors, which may explain its milder cognitive effects compared to benzodiazepines (20) in the CA1 region of rat hippocampal slices.

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Spatial learning and memory are critically dependent on hippocampal circuits (21). The hippocampus plays a central role in encoding, consolidating, and retrieving spatial information (22), and its activity is sensitive to GABAergic modulation (23). Long-term potentiation (LTP), a persistent increase in synaptic strength, is considered a key cellular mechanism underlying learning and memory (24). Because alterations in GABAergic tone can influence both the induction and maintenance of LTP (25), examining synaptic plasticity offers a valuable approach to understanding how zolpidem may modulate cognitive function.

In the laboratory, paired-pulse facilitation (PPF) ratios and induction of long-term potentiation (LTP) are fundamental protocols used to examine mechanisms of short-term and long-term synaptic plasticity, respectively (26). PPF is recorded to probe whether presynaptic mechanisms may underlie LTP expression, since LTP expression may involve increases in the probability of transmitter release from presynaptic terminals (27, 28).

Despite numerous behavioral studies, few investigations have simultaneously assessed both cognitive and electrophysiological outcomes following zolpidem administration. In particular, the differential effects of acute versus chronic exposure on hippocampal-dependent memory and synaptic plasticity remain unclear. Most prior studies have either focused solely on behavioral outcomes or evaluated only short-term effects, leaving a gap in understanding the long-term impact of zolpidem on neural function.

Therefore, in the present study, we aimed to investigate the effects of both acute and chronic zolpidem administration on spatial learning and memory, alongside electrophysiological assessment of hippocampal LTP as a potential underlying mechanism. By combining behavioral testing with synaptic plasticity measurements, this study aims to clarify how different durations of zolpidem exposure influence cognitive performance and hippocampal synaptic function.

Materials and Methods

Male Wistar rats 12 to 16 weeks old (weighing 200–250 g) were housed five per cage in a controlled environment with a 12-hr light/dark cycle and had ad libitum access to food and water.

All experimental procedures were approved by the ethical committee of Kashan University of Medical Sciences (IR.KAUMS.AEC.1402.023) and conducted in accordance with ethical guidelines to minimize animal suffering.

Treatment groups

The rats were randomly divided into three groups. The control group (n=9) received 0.9% saline with a solution volume of 1 ml/kg. Two groups received intraperitoneally

(IP) zolpidem either acutely (n=9) or chronically (n=8). The post-injection half-life of zolpidem in rodents is about 20 min (29, 30). The acute group received a single dose of 15 mg/kg zolpidem (31, 32) 30 min before the probe trial on day 4 of the behavioral experiments and 10 min before high-frequency stimulation (HFS) in electrophysiological recordings (33). The chronic group received 15 mg/kg zolpidem daily for a total of 30 days; 26 days before and 4 days during experiments (Figure 1). In this group, the last injections were given 30 min before maze performance (15) and 10 min before HFS in electrophysiological recordings.

Drug management

Zolpidem was provided in powder form (purchased from Aburaihan Pharmaceutical Company, Tehran, I.R. Iran). Zolpidem was dissolved in 0.9% saline with a solution volume of 1 ml/kg.

Behavioral testing

Behavioral experiments were done in a Morris water maze. The animals underwent two phases of maze performance, including acquisition and probe trial phases.

Acquisition phase

The maze consisted of a circular pool filled with water with a submerged escape platform. Before training, the rats were habituated to the test environment for 30 min. The rats were trained for three consecutive days with four trials per day. Each rat was released from a random quadrant and had 60 sec to find the platform. If it failed, it was guided to the platform and allowed to remain there for 5–10 sec. The time it took for the rat to find the platform was taken as an index of learning ability (34).

Probe trial

On the fourth day, the platform was removed to assess spatial memory consolidation. Rats were allowed to swim for 30 sec, and the time spent in the target quadrant served as an index of memory retention, with shorter times indicating impaired memory (35).

Electrophysiological recordings

Field excitatory postsynaptic potentials (fEPSPs) in the hippocampus were recorded based on our previously established protocol (36).

Surgical procedure

Rats were anesthetized using urethane and placed in a stereotaxic apparatus. Electrode placement was guided using coordinates for the Schaffer collateral and CA1 regions. Teflon-coated stainless-steel electrodes were used

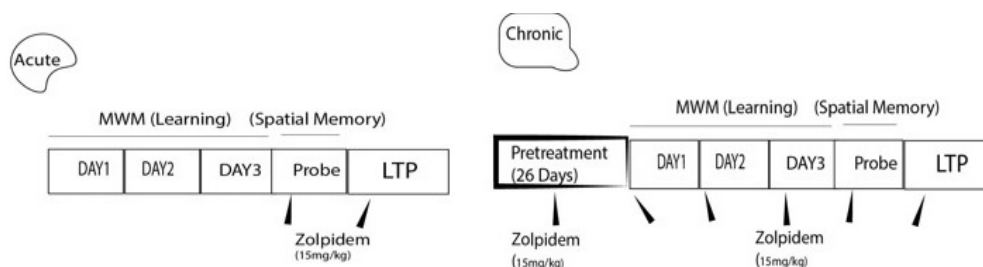


Figure 1. Summary of experiment flow in rats

The acute and chronic groups received zolpidem. For acute administration, zolpidem was administered intraperitoneally (IP) at 15 mg/kg, with injections occurring 30 min before maze performance and 10 min before HFS for electrophysiological (LTP) recordings. For chronic administration, zolpidem was administered at 15 mg/kg (IP) daily for 26 days before the MWM test, and injections continued throughout the behavioral and electrophysiological experiments.

MWM: Morris water maze.

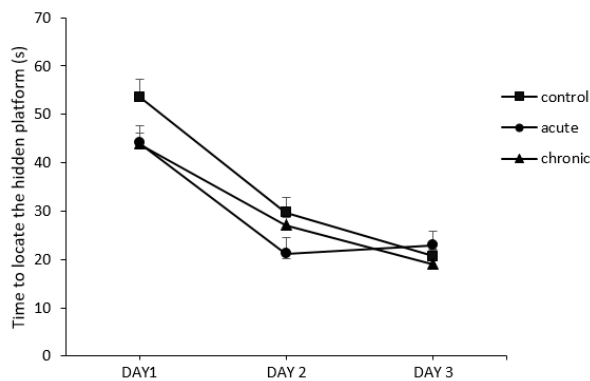


Figure 2. Effect of zolpidem on learning phase of spatial performance across different rat groups

The histograms illustrate the animals' performance during the three days of the acquisition phase, showing no significant differences in learning among the control (n=9) and chronic (n=8) groups ($P>0.97$).

for both stimulating and recording. A reference electrode was also placed externally to the brain.

Stimulation protocols

Paired pulse facilitation

Before baseline recording, PPF was assessed in the CA3–CA1 pathway to verify the integrity of NMDA receptor-dependent synaptic responses. Two stimuli separated by a 50-ms interstimulus interval were delivered, and recordings were continued only when the second fEPSP amplitude

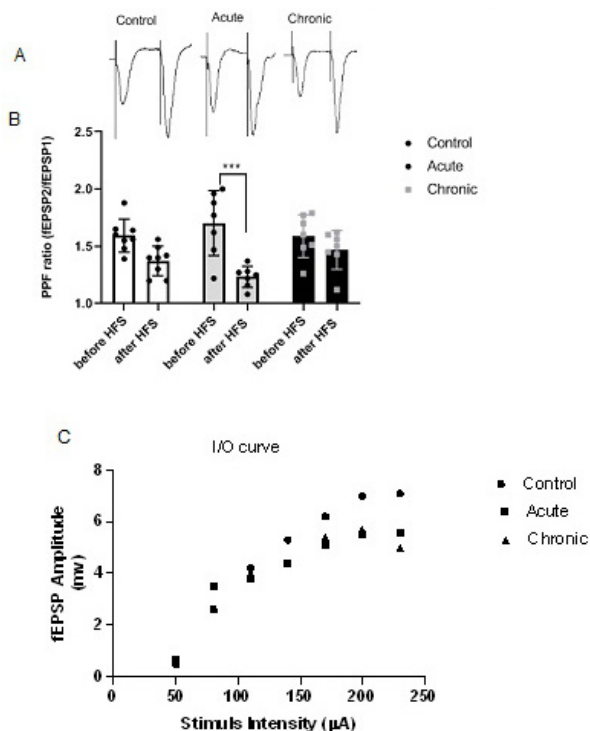


Figure 4. Effects of zolpidem treatment on PPF change in a rat model. PPF was measured before and 90 min after long-term potentiation induction in different groups. The PPF ratio was expressed as fEPSP2/fEPSP1. fEPSP1 is the response evoked by the first pulse, and fEPSP2 is the response evoked by the second pulse. A representative PPF trace is shown at the top of the graph (A). There was a significant difference in PPF before and after LTP induction in the acute group. There was no significant difference in PPF ratio in the other groups (B). (C) Shows input–output curves constructed from the fEPSP amplitude vs increasing stimulation intensities in the different groups. There was no significant difference between groups. PPF: Paired-pulse facilitation; fEPSP1: field excitatory postsynaptic potentials

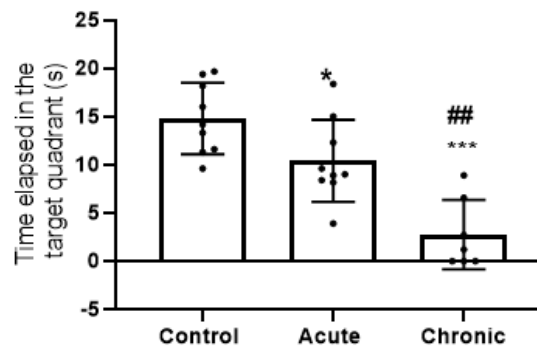


Figure 3. Effect of zolpidem on memory retention of spatial performance across different rat groups

The histogram shows that during the probe test, the acute and chronic groups exhibited significant differences compared to the control ($*P<0.05$, $***P<0.001$). Furthermore, the chronic group exhibited significantly greater spatial memory impairment than the acute group ($##P<0.002$).

was greater than the first, indicating PPF. Five paired-pulse responses were recorded and averaged at each interpulse interval. The PPF ratio was calculated as the amplitude of the second fEPSP divided by the amplitude of the first fEPSP (fEPSP2/fEPSP1). PPF was measured for 5 min before and after LTP induction.

I/O curve and baseline responses

Input–output (I/O) curves were generated by increasing the stimulus intensity in 5–10 μ A increments and recording the corresponding fEPSP amplitudes. The stimulus intensity was then adjusted to evoke an fEPSP with approximately 60% of the maximal response. Constant-current stimulation (two sweeps/min at 30-sec intervals) was controlled using computer software (Neurotrace, I.R. Iran) and delivered through a stimulator/isolator unit (WPI-A365). Test pulses were applied to the Schaffer collaterals, and fEPSPs were recorded from the CA1 region. After stable responses had been obtained, baseline fEPSPs (pre-tetanus responses) were recorded for 30 min.

Induction of LTP

Following baseline recordings, HFS was applied to induce LTP. LTP was induced by HFS of 100 Hz (10 bursts of 10 stimuli, 0.1 ms stimulus duration, and 2 s inter-burst intervals). Responses were recorded for 90 min after HFS. The magnitude of the fEPSPs was measured and normalized to baseline values.

Statistical analysis

Data were analyzed using SPSS 18.0 software for Windows. Two-way ANOVA followed by Tukey's *post hoc* test was conducted to assess significant differences among the groups. Column scatter plots were generated using GraphPad Prism version 10.6. $P<0.05$ was considered statistically significant. All values are presented as mean $\pm$ SEM.

Results

Spatial learning and memory

Acquisition phase

Three days of training in the water maze showed no significant differences ($F_{2, 321} = 0.027$; $P<0.097$) between different groups. Chronic injection of zolpidem showed no difference in maze performance compared with their

control counterparts (Figure 2).

Probe trial phase

In the probe trial test, the animals displayed a significant variation in the time spent in the target quadrant ($F(2,23) = 19.51$, $P < 0.001$). Compared with the control group, the acute zolpidem group showed a significant impairment in spatial memory ($P < 0.05$). Moreover, chronic zolpidem administration resulted in a significantly greater impairment in spatial memory than both the acute ($P < 0.01$) and control ($P < 0.001$) groups (Figure 3).

Electrophysiological recordings

PPF ratio

In this study, the PPF ratio (% change) was measured before and after induction of LTP. Results showed that the PPF ratio was significantly decreased in the acute group before and after induction of LTP ($F(5, 38) = 6.7$; $P < 0.001$). There was no significant difference in PPF ratio in the control ($F(5, 38) = 6.7$, $P < 0.14$) and chronic ($F(5, 38) = 6.7$, $P < 0.8$) groups before and after induction of LTP. (Figure 4A and B). No differences were observed in input-output curve between groups (Figure 4C).

Baseline fEPSPs

Baseline fEPSPs were recorded in the CA1 region of the

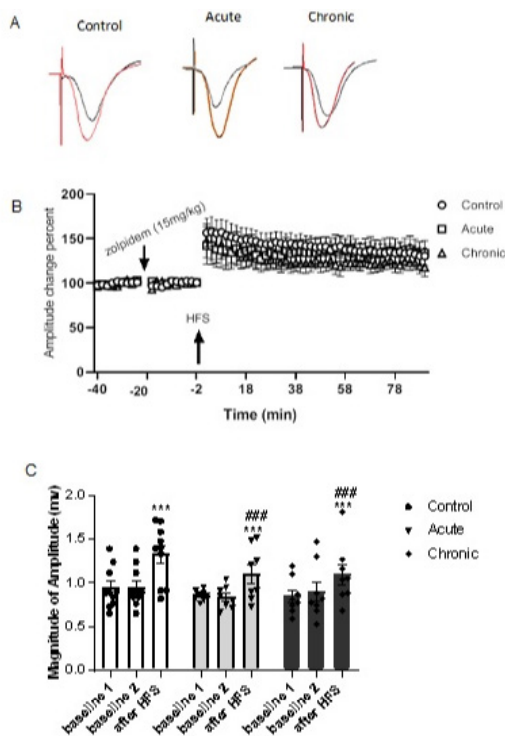


Figure 5. Induction of LTP in the rat hippocampal CA1 area. Sample traces of a single evoked fEPSP recorded in the CA3-CA1 pathway of the hippocampus (A). Time-dependent changes in the fEPSP amplitude after HFS application normalized to basal responses in different groups (B). The application of HFS on the Schaffer collaterals resulted in significant LTP across all groups, with increases of 56%, 42%, and 47% in the control, acute, and chronic groups, respectively (C). Although the potentiation decreased over time (B), the circuit remained potentiated throughout the recording period, demonstrating a significant difference between the fEPSPs before and after HFS in each group ($***P < 0.001$). $###P < 0.001$, acute and chronic treatment groups versus control group. "Baseline 1" represents the baseline responses recorded before zolpidem administration, whereas "Baseline 2" represents the baseline responses recorded after zolpidem administration, and "after HFS" represents the mean fEPSP recorded over the 90-min period following HFS. LTP: Long-term potentiation; fEPSP1: field excitatory postsynaptic potentials; HFS: High-frequency stimulation

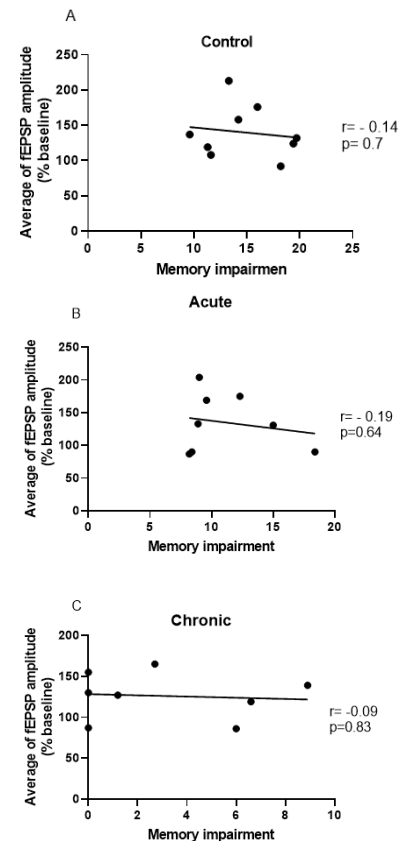


Figure 6. Correlation between mean fEPSP amplitude and probe trial performance, as an index of spatial memory retention, in the control, acute, and chronic zolpidem-treated rat groups (A–C). Pearson's correlation analysis revealed no significant correlation between mean fEPSP amplitude and probe trial performance in any of the groups. Pearson's correlation coefficient (r) and the corresponding P values are shown in each panel. fEPSP1: field excitatory postsynaptic potentials

hippocampus in response to stimulation of the Schaffer collaterals. Baseline measurements taken before and after zolpidem administration indicated no significant differences among the testing groups ($P > 0.65$). Additionally, analysis of variance showed no significant differences ($P > 0.45$) in baseline fEPSP magnitudes between the groups (Figure 5A).

Induction of LTP

To investigate the impact of the zolpidem injection on hippocampal long-term synaptic plasticity, we analyzed CA3-CA1 pathway LTP in control, acute, and chronic zolpidem groups (Figure 5). The correlation between hippocampal synaptic plasticity (LTP) and probe trial performance, as an index of spatial memory retention, in control and zolpidem-treated groups is shown in Figure 6. At the onset of induction, HFS applied to the Schaffer collaterals produced significant long-term potentiation (LTP) of 56% in the hippocampal CA1 area of control animals (8 out of 10 animals). Tetanic stimulation resulted in a comparable significant increase in LTP, with 42% in the acute and 47% in the chronic groups, as indicated by post-HFS fEPSP magnitudes observed in 3 out of 9 acute rats ($P < 0.001$) and 5 out of 8 chronic rats ($P < 0.001$). In all three groups, although the enhancement declined over time, the circuit remained potentiated throughout the recording period, demonstrating a significant difference between the pre- and post-HFS fEPSPs ($P < 0.001$). Ninety min after

recording, the levels of potentiation decreased to 42% in the control group, 35% in the acute and 26% in the chronic groups. After this period, analysis of variance revealed that the mean magnitude in the acute and chronic groups had significantly declined compared to the control group ($P < 0.001$). Additionally, no significant differences in the extent of LTP induction were observed between the acute and chronic groups after 90 min. Figure 5B and C depicts the pre- and post-tetanus traces along with the magnitude changes of the fEPSPs, respectively.

Discussion

In the present study, we investigated the effects of acute and chronic zolpidem administration on spatial learning and memory as well as hippocampal long-term potentiation (LTP). We combined behavioral testing with *in vivo* electrophysiological recordings to examine the relationship between behavioral deficits and synaptic dysfunction in the CA3-CA1 pathway. Pearson's correlation analysis revealed no significant correlation between behavioral performance and LTP. Memory retention in the probe trial was significantly impaired in both the acute and chronic treatment groups, with the chronic group exhibiting significantly greater memory impairment than the acute group. In addition, zolpidem significantly decreased the PPF ratio only in the acute treatment group, whereas no significant changes were observed in the control or chronic treatment groups. PPF is considered an index of presynaptic neurotransmitter release (26). These findings suggest that acute zolpidem administration has a more pronounced effect on presynaptic function than chronic administration. Further studies are required to elucidate the mechanisms underlying the differential effects of acute and chronic zolpidem administration on PPF and synaptic plasticity.

Electrophysiological recordings from the CA1 region of the hippocampus revealed that both acute and chronic zolpidem groups exhibited a significant reduction in LTP compared to controls.

Our findings are consistent with previous studies in both humans and animal models showing that zolpidem can impair cognitive function and synaptic plasticity. For example, Morairty *et al.* reported that acute administration of zolpidem (100 mg/kg, PO) impaired spatial memory in rats in the MWM task (31). Miroslav *et al.* demonstrated that doses of 1–3 mg/kg, administered 20 min before avoidance learning, reduced memory retention in mice (37). Zanin KA *et al.* observed that acute doses of 5 and 10 mg/kg of zolpidem disrupted aspects of memory formation in rodents without fully abolishing long-term memory (38). In humans, Gray *et al.* showed that 10 mg zolpidem administered half an hour before bedtime reduced both short- and long-term recall in older adults (39), and Danielle *et al.* reported that 5 mg zolpidem administered 10 min before sleep impaired working memory and increased fall risk in elderly individuals (14).

At the molecular level, zolpidem primarily augments inhibitory neurotransmission via GABA_A receptors (40, 41). The greater reduction in spatial memory observed in the chronic group compared to the acute group suggests cumulative effects of prolonged exposure and potential adaptive changes in GABA-A receptor function (42), further suppressing excitatory signaling and impairing spatial memory. Chronic zolpidem exposure may lead

to compensatory downregulation of GABA-A receptor subunits or alterations in receptor desensitization, further dampening excitatory signaling and impairing spatial memory (43).

Long-term potentiation as a cellular mechanism of long-standing memory depends on synaptic strengthening mediated by NMDA receptor-dependent calcium influx and CaMKII activation (44). Zolpidem-induced GABAergic inhibition reduces excitatory signaling, resulting in decreased LTP magnitude. Supporting this, Julie *et al.* reported reduced cortical neuronal plasticity in cats after 10 mg/kg zolpidem (45). At the same time, Josien *et al.* demonstrated that acute zolpidem restored LTP in tau-mutant mice but had no significant effect in normal mice (33).

As a limitation of our work, urethane is known to have potent GABAergic properties (46). The use of urethane anesthesia during electrophysiological recordings may interact with zolpidem's modulation of GABA-A receptors. In the present study, this combined effect might either mask or exaggerate the true synaptic changes induced by zolpidem, potentially affecting the accuracy of LTP measurements. Another limitation of the present study is that LTP was induced in the animals that had been trained for the MWM test. In fact, the MWM test activates synaptic transmission and induces LTP in the hippocampal synapses. Therefore, the ability of synapses to show LTP in response to HFS decreases and, in fact, metaplasticity will occur. To see whether LTP is a mechanism of memory impairment, LTP induction should be evaluated in a group of animals that received zolpidem in acute or chronic situations but were not tested on the MWM test. Therefore, caution is warranted when interpreting these electrophysiological results, and future studies may consider using alternative protocols to avoid this confounding factor.

Conclusion

Both acute and chronic zolpidem administration impaired hippocampus-dependent spatial memory and reduced hippocampal LTP. However, chronic treatment produced significantly greater memory impairment than acute treatment, suggesting cumulative adverse effects of prolonged zolpidem exposure on cognitive function. In contrast, the PPF ratio was significantly decreased only after acute zolpidem administration, indicating a greater effect on presynaptic neurotransmitter release during the acute phase. Furthermore, no significant correlation was observed between behavioral performance and LTP, indicating that spatial memory impairment cannot be explained solely by alterations in hippocampal synaptic plasticity. Overall, these findings provide novel *in vivo* evidence that acute and chronic zolpidem differentially affect presynaptic function, while both impair hippocampal synaptic plasticity and spatial memory.

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Authors' Contributions

H B was responsible for designing the project. Z R conducted the experiments, analyzed the data, and authored the manuscript. M S and H B contributed significantly to refining and finalizing the document.

Conflicts of Interest

No conflicts of interest.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

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