

Effects of Histamine H4 Receptor Antagonist on Cisplatin-induced Sleep Fragmentation in Mice

Kouichi Yamamoto

kouichi_yamamoto@morinomiya-u.ac.jp

Morinomiya University of Medical Sciences

Keiko Yamamoto

Morinomiya University of Medical Sciences

Article

Keywords: cisplatin, histamine H4 receptor, mice, piezoelectric sleep monitoring, sleep continuity, sleep fragmentation

Posted Date: September 24th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10922299/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Purpose: Cisplatin is widely applied to treat patients with various solid tumors, but such use is frequently associated with fatigue, malaise, and sleep disturbances. The present study examined whether cisplatin alters sleep quantity and continuity in mice, and if pharmacological modulation of the histamine H4 receptor (H4R) can attenuate such changes.

Methods: Sleep was monitored non-invasively using a piezoelectric system over three consecutive days. Total sleep time, number of sleep episodes, and mean sleep episode duration were analyzed separately during dark and light phases.

Results: Cisplatin increased total sleep time during the dark phase on Days 2 and 3, while no clear change in this total was detected during the light phase. In contrast, cisplatin consistently increased the number of sleep episodes and shortened the mean sleep episode duration during both phases, indicating reduced sleep continuity. The H4R antagonist JNJ7777120 partially attenuated these changes, particularly the increase in episodes and shortening of their duration.

Conclusion: These findings suggest that cisplatin use leads to a fragmented sleep pattern rather than simply reducing sleep quantity, and that H4R-associated pathways may contribute to the chemotherapy-induced disruption of sleep organization.

1. Introduction

Sleep disturbance and fatigue are common in patients with cancer and may be exacerbated during chemotherapy [1]. Alterations in sleep can adversely affect the quality of life and may be associated with fatigue, psychological distress, and other treatment-related symptoms. Clinical studies have reported sleep quality deterioration during chemotherapy [2]; however, the effects of individual chemotherapeutic agents on sleep-wake behavior and the mechanisms underlying these changes remain incompletely understood.

Cisplatin is a platinum-based chemotherapeutic agent widely used for the treatment of patients with various solid tumors. Despite its clinical efficacy, cisplatin treatment is associated with multiple adverse effects, including nausea, vomiting, anorexia, fatigue, and other symptoms linked to treatment-related malaise [3, 4]. These adverse responses involve complex interactions among peripheral inflammatory signals and central neural pathways. The histamine H4 receptor (H4R) is involved in the regulation of immune and inflammatory responses, and pharmacological blockade of H4R has anti-inflammatory effects [5–7]. Previous studies by our group demonstrated cisplatin-associated inflammatory responses, including tumor necrosis factor (TNF)- α production [8], and showed that H4R antagonism ameliorated cisplatin-induced anorexia in mice [9]. Furthermore, we reported that orexinergic and histaminergic pathways may participate in these effects [10]. These observations raise the possibility that H4R-associated mechanisms contribute to behavioral alterations induced by cisplatin beyond the regulation of food intake.

Inflammatory signaling is closely associated with sleep regulation [11]. Cytokines and other inflammatory mediators can modify sleep-wake behavior, whereas the disruption of sleep itself can influence inflammatory responses. Importantly, sleep disturbance cannot be characterized solely by changes in the total sleep duration. Sleep continuity represents another important dimension of sleep and can be assessed by the frequency and duration of individual sleep episodes. An increase in the number of sleep episodes accompanied by shortening of individual episodes indicates reduced sleep continuity and is consistent with a fragmented sleep pattern. This distinction may be particularly relevant to chemotherapy-induced behavioral alterations.

In our previous study using facial-expression analysis in rats, cisplatin increased the duration of eye closure associated with a nausea-like response [12]. However, prolonged eye closure or behavioral inactivity does not necessarily represent physiological sleep. Therefore, objective assessment of sleep behavior is necessary to determine whether cisplatin affects the quantity, continuity, or temporal organization of sleep.

In the present study, we investigated the effects of cisplatin on sleep behavior in mice using a non-invasive piezoelectric sleep monitoring system. Sleep was evaluated separately during dark and light phases over three consecutive days. Total sleep time was used as an index of sleep quantity, whereas the number of sleep episodes and mean sleep episode duration were used to assess sleep continuity. Hourly sleep profiles were additionally examined to characterize the temporal distribution of sleep. We further investigated whether pretreatment with an H4R antagonist modified cisplatin-induced alterations in sleep. We hypothesized that cisplatin would disrupt sleep continuity and that H4R antagonism would attenuate such alterations.

2. Materials and Methods

2.1 Animals

All experiments were approved by the Animal Care Committee of Morinomiya University of Medical Sciences (2023A014 and 2023A015) and were performed in accordance with the relevant institutional guidelines and regulations. The study is reported in accordance with the ARRIVE guidelines. Male BALB/c mice were obtained from Japan SLC (Shizuoka, Japan). About six-week-old mice were housed in individual home cages in a room with a regular light/dark cycle (lights on 0600 h – 1800 h) at a constant temperature (approximately 24°C) and humidity (approximately 50%). They were allowed free access to tap water and commercially available standard chow (MF, Oriental Yeast, Osaka, Japan).

2.2 Assessment of sleep behavior

Sleep-wake behavior was monitored using a non-invasive piezoelectric sleep monitoring system (PiezoSleep®, Signal Solutions, LLC, Lexington, Kentucky, USA). Mice were individually housed in recording cages (14 x 21 x 12 cm), and sleep and wake states were automatically classified using the software supplied with the PiezoSleep system based on piezoelectric signals generated by body

movements and respiratory activity (Sleep Stat 4 Base version 4.3.16., Signal Solutions). The resulting data were exported to Microsoft Excel for subsequent data processing. Sleep behavior was evaluated over three consecutive days and analyzed separately for dark and light phases. Total sleep time was calculated as the cumulative duration of sleep during each 12-h period and expressed in seconds. The number of sleep episodes was defined as the number of discrete sleep episodes detected during each 12-h period.

Mean sleep episode duration [s/episode] was calculated as the total sleep time (s) divided by number of sleep episodes. Total sleep time was used as an index of sleep quantity, whereas the sleep episode number and mean sleep episode duration were used as indices of sleep continuity. To evaluate the temporal distribution of sleep, its duration was additionally calculated at 1-h intervals and expressed as minutes of sleep per hour.

2.3 Experimental groups and drug administration

Mice were randomly assigned to four groups: (1) control, (2) cisplatin, (3) cisplatin + low dose H4R antagonist, and (4) cisplatin + high dose H4R antagonist. Mice were adapted to the experimental environment for at least 14 days. On the day of the experiment, mice intraperitoneally (i.p.) received cisplatin (7.5 mg/kg) at 1800 h. It was dissolved in physiological saline just prior to administration. Control animals received an i.p. injection of saline (1 mL/100 g of body weight). The H4R antagonist JNJ7777120 (5 or 10 mg/kg) was administered at 15 min before and 24 and 48 h after cisplatin administration. Control and cisplatin groups each consisted of 11 mice, whereas cisplatin + low dose H4R antagonist and cisplatin + high dose H4R antagonist groups each consisted of 10 mice. No formal a priori sample size calculation was performed. Sample sizes were determined empirically based on our experience with similar experiments. Six mice were excluded from the analysis because sleep data could not be obtained. No other animals or data were excluded from the analysis. JNJ7777120 was dissolved or diluted in saline containing 0.5% dimethyl sulfoxide (DMSO). All mice received saline containing 0.5% DMSO as the vehicle. At the end of the experiment, mice were euthanized by inhalation of an overdose of sevoflurane without prior administration of another anesthetic agent. Drug administration was not performed under blinded conditions; however, sleep-wake classification was performed automatically by the Sleep Stat software.

2.4 Drugs

Cisplatin (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan), JNJ7777120 (Selleck Chemicals LLC, Houston, TX, USA), and sevoflurane (Nikko Pharmaceutical Company, Gifu, Japan) were purchased through a pharmaceutical agency (Katayama Chemical Industries, Osaka, Japan). The indicated doses are those of the free base. All drugs were prepared immediately before use.

2.5 Statistical analysis

Data are expressed as the mean $\pm$ SD. Statistical analyses were performed using GraphPad Prism version 11.0.2 (GraphPad Software, Boston, MA, USA). The total sleep time, number of sleep episodes,

and mean sleep episode duration were analyzed separately for dark and light phases using two-way repeated-measures analysis of variance (ANOVA), with treatment and time (Days 1–3) as the between- and within-subject factors, respectively. Geisser-Greenhouse correction was applied without assuming sphericity. Šídák's multiple-comparisons test was applied for prespecified comparisons between the cisplatin group and control, cisplatin + low dose H4R antagonist, and cisplatin + high dose H4R antagonist groups at each time-point. A value of $P < 0.05$ was considered significant.

2.6 Generative AI statement

The authors declare that ChatGPT (OpenAI) was used in the creation of this manuscript to assist with language editing, manuscript organization, and literature identification. All AI-assisted content was reviewed and revised by the authors, who take full responsibility for the integrity, accuracy, and final content of the manuscript.

3. Results

3.1 Cisplatin-induced alteration of total sleep time

Cisplatin increased the total sleep time during the dark but not light phase. As shown in Fig. 1 (A), during the dark phase, two-way repeated-measures ANOVA revealed significant main effects of treatment ($P = 0.0021$) and time ($P = 0.0053$), whereas the treatment $\times$ time interaction was not significant ($P = 0.0859$). Šídák's multiple-comparisons test showed that the total sleep time was significantly greater in the cisplatin than control group on Days 2 ($P = 0.0079$) and 3 ($P = 0.0295$), whereas the difference did not reach significance on Day 1 ($P = 0.0864$). Thus, cisplatin increased sleep during the normally active dark phase, particularly on Days 2 and 3. The H4R antagonist did not significantly alter the total sleep time compared with cisplatin alone at most observation points. An exception was observed on Day 3, when the low dose group showed significantly lower total sleep time than the cisplatin group ($P = 0.0161$). As presented in Fig. 1 (B), during the light phase, neither the treatment ($P = 0.1133$), time ($P = 0.2601$), nor treatment $\times$ time interaction ($P = 0.4271$) significantly affected the total sleep time. No significant differences were detected in the prespecified multiple comparisons on any observation day.

3.2 Cisplatin-induced alteration in number of sleep episodes

Cisplatin increased the number of sleep episodes. As presented in Fig. 2 (A), during the dark phase, significant main effects of treatment ($P < 0.0001$) and time ($P = 0.0002$) were observed, whereas the treatment $\times$ time interaction was not significant ($P = 0.2394$). Cisplatin significantly increased the number of sleep episodes compared with control on Days 1 ($P = 0.0034$), 2 ($P < 0.0001$), and 3 ($P = 0.0001$). The high dose H4R antagonist significantly reduced the number of sleep episodes compared with cisplatin alone on all three days (Day 1, $P = 0.0040$; Day 2, $P = 0.0471$; Day 3, $P = 0.0059$). In contrast, the low dose did not significantly affect the episode number. As shown in Fig. 2 (B), during the light phase, a significant main effect of treatment was detected ($P < 0.0001$), whereas neither the time ($P =$

0.0565) nor treatment $\times$ time interaction ($P = 0.2004$) was significant. Cisplatin significantly increased the sleep episode number compared with control on all three days (Day 1, $P = 0.0005$; Day 2, $P = 0.0028$; Day 3, $P = 0.0008$). On Day 3, both the low and high dose H4R antagonist groups exhibited significantly fewer sleep episodes than the cisplatin group ($P = 0.0132$ and $P = 0.0009$, respectively).

3.3 Cisplatin-induced alteration of mean sleep episode duration

Cisplatin shortened the mean sleep episode duration. As can be noted in Fig. 3 (A), during the dark phase, significant main effects of treatment ($P < 0.0001$) and time ($P = 0.0049$) were detected, whereas the treatment $\times$ time interaction was not significant ($P = 0.1483$). Cisplatin significantly shortened the mean sleep episode duration compared with control on Days 1 ($P = 0.0022$), 2 ($P = 0.0036$), and 3 ($P = 0.0066$). The high dose of the H4R antagonist significantly increased the mean sleep episode duration compared with cisplatin alone on Days 1 ($P = 0.0062$) and 3 ($P = 0.0480$), whereas no significant effect was detected on Day 2. The low dose did not significantly affect the mean sleep episode duration. As shown in Fig. 3 (B), during the light phase, a significant main effect of treatment was observed ($P = 0.0069$), whereas neither the time ($P = 0.1153$) nor treatment $\times$ time interaction ($P = 0.5731$) was significant. The mean sleep episode duration was significantly shorter in cisplatin-treated mice than controls on Days 1 ($P = 0.0178$), 2 ($P = 0.0468$), and 3 ($P = 0.0155$). The high dose H4R antagonist significantly increased the mean sleep episode duration compared with cisplatin alone on Day 3 ($P = 0.0088$).

Collectively, cisplatin consistently increased the number of sleep episodes while shortening their mean duration during both dark and light phases. Thus, despite the absence of a reduction in the total sleep time, cisplatin markedly reduced sleep continuity and induced a sleep pattern consistent with increased fragmentation. H4R antagonism, particularly at the higher dose, partially attenuated these alterations.

To further illustrate these changes in the temporal distribution of sleep, hourly sleep profiles over the 24-h light–dark cycle on Days 1–3 are presented in Supplementary Fig. 1.

4. Discussion

The key findings of the present study are summarized in Table 1. The principal finding was that cisplatin markedly disrupted sleep continuity in mice rather than simply reducing sleep quantity. Cisplatin consistently increased the number of sleep episodes and shortened the mean sleep episode duration during both dark and light phases over the three-day observation period. Moreover, the total sleep time was increased during the dark phase on Days 2 and 3 but was not significantly altered during the light phase. Thus, the cisplatin-induced increase in sleep during the normally active phase did not represent consolidated sleep but was accompanied by frequent and shortened sleep episodes. These findings indicate that assessment of the total sleep time alone does not adequately characterize cisplatin-induced alterations in sleep.

Sleep quantity and continuity represent distinct aspects of sleep behavior [13]. An animal may exhibit a preserved cumulative sleep duration despite frequent transitions between sleep and wakefulness, indicating that sleep quantity alone does not necessarily reflect sleep continuity [14, 15]. In the present study, the combination of an increased sleep episode number and shortened episode duration provides evidence of impaired sleep continuity following cisplatin treatment. Importantly, this pattern was observed during both dark and light phases, suggesting that cisplatin-induced disruption of sleep organization was not restricted to a single circadian phase. Such a pattern of frequent, shortened sleep episodes is consistent with increased sleep fragmentation.

The increase in total sleep time during the dark phase is particularly noteworthy because mice are nocturnal and normally exhibit greater wakefulness during this period [16]. Increased sleep during the normally active phase may therefore reflect disruption of the normal temporal organization of sleep and wakefulness rather than improved sleep. Sleep–wake disturbances have also been reported in patients undergoing chemotherapy. Liu et al. [17] reported that the objective total sleep time in patients increased compared with baseline measurements during the course of chemotherapy, although their subjective sleep quality was poor at the baseline and remained unchanged throughout treatment. Furthermore, patients with breast cancer have shown that chemotherapy may be accompanied by increased daytime and night-time sleep despite worsening fatigue, as well as disruption of sleep–wake activity rhythms [17, 18]. These observations suggest that increased or preserved sleep duration does not necessarily indicate normal sleep organization. Although any direct comparison between clinical observations and the present animal model should be made cautiously, the present findings may show the usefulness of the experimental model for investigating treatment-associated disruption of sleep–wake organization. This interpretation is also relevant to our previous observation that cisplatin increased eye closure in rats during nausea-like behavior [12]. Although prolonged eye closure may superficially resemble sleep, such closure alone does not indicate the presence of physiological sleep. The present study extends observations by objectively assessing sleep behavior, and demonstrates that cisplatin increases sleep during the normally active phase while simultaneously inducing frequent and shortened sleep episodes.

Mechanisms underlying cisplatin-induced disruption of sleep continuity remain unclear. Inflammatory signaling may influence not only sleep quantity but also the organization and continuity of sleep. In this context, Borniger et al. [19] reported that administrations of doxorubicin and cyclophosphamide increased sleep during the normally active dark phase in mice while simultaneously inducing fragmented, low-quality sleep; these alterations were accompanied by increased hypothalamic IL-6 expression. Such findings are particularly relevant to our observation that cisplatin increased the total sleep time during the dark phase while increasing sleep episodes and shortening their duration. Both findings suggest that chemotherapy-associated increases in sleep during the active phase may coexist with impaired sleep continuity, although the chemotherapeutic agents and experimental conditions differed between the two studies. Cisplatin has been shown to induce proinflammatory signaling [20], and proinflammatory cytokines such as TNF- α and IL-6 are known to participate in the regulation of sleep and sickness-related behavior [21–23]. We previously demonstrated that cisplatin induces TNF- α production in murine macrophages [8]. Thus, cisplatin-induced inflammatory signaling could potentially

contribute to both altered sleep propensity and reduced sleep continuity. However, because inflammatory mediators were not directly measured in the present study, this interpretation remains hypothetical; thus, further studies are required to determine whether TNF- α , IL-6, or other inflammatory mediators contribute to cisplatin-induced sleep fragmentation.

Another important finding of the present study was that H4R antagonism partially attenuated cisplatin-induced disruption of sleep continuity. The high dose of JNJ7777120 consistently reduced the cisplatin-induced increase in sleep episode number during the dark phase and increased the mean sleep episode duration on Days 1 and 3. During the light phase, significant effects of H4R antagonism were more evident on Day 3. In contrast, the antagonist exerted relatively limited effects on the total sleep time. These findings suggest that H4R antagonism may preferentially affect the organization and continuity of sleep rather than simply altering sleep quantity. We previously demonstrated that H4R antagonism suppressed cisplatin-induced TNF- α mRNA expression [9]. Elevated TNF- α signaling has been associated with changes in normal sleep regulation and disruption of sleep–wake organization [21]. Moreover, Zhan et al. demonstrated that repeated TNF- α administration induced abnormal sleep patterns and sleep fragmentation in mice [24]. Given the established involvement of TNF- α in sleep regulation, the anti-inflammatory action of H4R antagonism may therefore provide one possible explanation for the partial attenuation of cisplatin-induced sleep disruption noted in the present study.

Zhan et al. demonstrated that TNF- α reduces hypothalamic orexin expression [24]. We also previously reported that the orexinergic and histaminergic pathways were involved in the ameliorative effect of H4R antagonism on cisplatin-induced anorexia [10]. Cisplatin significantly decreased prepro-orexin (PPO) mRNA expression in the hypothalamus of mice, and this decrease was maintained at 50 h after cisplatin administration, whereas JNJ7777120 significantly attenuated the cisplatin-induced reduction in PPO mRNA expression. Because the orexinergic and histaminergic systems play important and complementary roles in the maintenance of wakefulness and sleep–wake stability [25–27], modulation of these pathways may contribute to the effects of H4R antagonism observed in the present study. Orexin neurons provide excitatory input to histaminergic neurons in the tuberomammillary nucleus, and disruption of either orexinergic or histaminergic signaling has been associated with increased sleep–wake fragmentation. Hara et al. reported that genetic ablation of orexin neurons resulted in hypophagia in mice [28]. These findings raise the possibility that attenuation of cisplatin-induced sleep disruption may contribute to the recovery of food intake associated with H4R antagonism. Such antagonism in the present study exerted relatively limited effects on the total sleep time but more clearly attenuated the increase in episode number and shortening of the duration. These findings raise the possibility that H4R antagonism may influence the stability of sleep–wake states rather than simply altering overall sleep quantity. However, because orexinergic and histaminergic activity was not directly assessed in the present study, this possibility remains to be investigated.

Several limitations should be acknowledged. First, sleep was assessed using a non-invasive piezoelectric monitoring system rather than electroencephalography and electromyography; therefore, individual sleep stages such as rapid eye movement (REM) and non-REM sleep could not be

distinguished. Second, inflammatory mediators and neural activity within histaminergic or orexinergic pathways were not directly measured in the present study. Third, although increased episode number and shortened episode duration are consistent with reduced sleep continuity and increased fragmentation, further electrophysiological studies are required to characterize changes in sleep architecture in greater detail.

In conclusion, cisplatin altered both the quantity and continuity of sleep in mice. It also increased sleep during the normally active dark phase while consistently increasing the sleep episode number and shortening the mean duration during both dark and light phases. These findings indicate that cisplatin disrupts sleep continuity and induces a fragmented sleep pattern rather than simply reducing sleep duration. H4R antagonism, particularly at the higher dose, partially attenuated these alterations in sleep continuity. H4R-associated pathways may therefore represent a potential pharmacological target to counter chemotherapy-induced disturbances in sleep organization.

Abbreviations

ANOVA: analysis of variance

DMSO: dimethyl sulfoxide

H4R: histamine H4 receptor

IL: interleukin

PPO: prepro-orexin

REM: rapid eye movement

SD: standard deviation

TNF- α : tumor necrosis factor- α

Declarations

Funding

This study was supported by JSPS KAKENHI Grant Number JP23K11441.

Author Contributions

Kouichi Yamamoto conceived and designed the study, performed the experiments, analyzed the data, and wrote the original draft of the manuscript. Keiko Yamamoto performed the experiments, analyzed the data, and reviewed and revised the manuscript. Both authors read and approved the final manuscript.

Competing Interests

The authors declare no competing interests.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Al Maqbali, M., Al Sinani, M., Alsayed, A. & Gleason, A. M. Prevalence of sleep disturbance in patients with cancer: a systematic review and meta-analysis. *Clin. Nurs. Res.* **31**, 1107–1123 (2022).
2. Carson, E. K. et al. The impact of breast cancer treatment on sleep disturbance: a systematic review. *Breast Cancer Res. Treat.* **215**, 48 (2025).
3. Oun, R., Moussa, Y. E. & Wheate, N. J. The side effects of platinum-based chemotherapy drugs: a review for chemists. *Dalton Trans.* **47**, 6645–6653 (2018).
4. Malik, N. M. et al. Behavioural and hypothalamic molecular effects of the anti-cancer agent cisplatin in the rat: a model of chemotherapy-related malaise? *Pharmacol. Biochem. Behav.* **83**, 9–20 (2006).
5. Zhang, M., Thurmond, R. L. & Dunford, P. J. The histamine H4 receptor: a novel modulator of inflammatory and immune disorders. *Pharmacol. Ther.* **113**, 594–606 (2007).
6. Walter, M., Kottke, T. & Stark, H. The histamine H4 receptor: targeting inflammatory disorders. *Eur. J. Pharmacol.* **668**, 1–5 (2011).
7. Cowden, J. M. et al. Antagonism of the histamine H4 receptor reduces LPS-induced TNF production in vivo. *Inflamm. Res.* **62**, 599–607 (2013).
8. Kim, S., Yamamoto, K., Nakamura, Y., Ootoy, Y. & Yamatodani, A. A possible mechanism of cisplatin-induced tumor necrosis factor (TNF)- α production in murine macrophages. *Pharmacol. Pharm.* **4**, 146–151 (2013).
9. Yamamoto, K., Okui, R. & Yamatodani, A. Effects of a histamine H4 receptor antagonist on cisplatin-induced anorexia in mice. *Neurosci. Lett.* **676**, 103–107 (2018).
10. Yamamoto, K., Okui, R. & Yamatodani, A. Activation of orexinergic and histaminergic pathway involved in therapeutic effect of histamine H4 receptor antagonist against cisplatin-induced anorexia in mice. *Naunyn Schmiedeberg's Arch. Pharmacol.* **392**, 925–936 (2019).
11. Irwin, M. R. Sleep and inflammation: partners in sickness and in health. *Nat. Rev. Immunol.* **19**, 702–715 (2019).
12. Yamamoto, K., Tatsutani, S. & Ishida, T. Detection of nausea-like response in rats by monitoring facial expression. *Front. Pharmacol.* **7**, 534 (2017).
13. Laffan, A., Caffo, B., Swihart, B. J. & Punjabi, N. M. Utility of sleep stage transitions in assessing sleep continuity. *Sleep* **33**, 1681–1686 (2010).
14. McKenna, J. T. et al. Sleep fragmentation elevates behavioral, electrographic and neurochemical measures of sleepiness. *Neuroscience* **146**, 1462–1473 (2007).

15. Ramesh, V. et al. Disrupted sleep without sleep curtailment induces sleepiness and cognitive dysfunction via the tumor necrosis factor- α pathway. *J. Neuroinflammation*. **9**, 91 (2012).
16. Hiyoshi, H., Terao, A., Okamatsu-Ogura, Y. & Kimura, K. Characteristics of sleep and wakefulness in wild-derived inbred mice. *Exp. Anim.* **63**, 205–213 (2014).
17. Liu, L. et al. The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. *Sleep* **35**, 237–245 (2012).
18. Savard, J. et al. Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. *Sleep* **32**, 1155–1160 (2009).
19. Borniger, J. C., Gaudier-Diaz, M. M., Zhang, N., Nelson, R. J. & DeVries, A. C. Cytotoxic chemotherapy increases sleep and sleep fragmentation in non-tumor-bearing mice. *Brain Behav. Immun.* **47**, 218–227 (2015).
20. Domingo, I. K., Latif, A. & Bhavsar, A. P. Pro-inflammatory signalling PRRopels cisplatin-induced toxicity. *Int. J. Mol. Sci.* **23**, 7227 (2022).
21. Rockstrom, M. D. et al. Tumor necrosis factor alpha in sleep regulation. *Sleep. Med. Rev.* **40**, 69–78 (2018).
22. Veler, H. Sleep and inflammation: bidirectional relationship. *Sleep. Med. Clin.* **18**, 213–218 (2023).
23. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. & Kelley, K. W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* **9**, 46–56 (2008).
24. Zhan, S. et al. Molecular mechanism of tumour necrosis factor alpha regulates hypocretin (orexin) expression, sleep and behaviour. *J. Cell. Mol. Med.* **23**, 6822–6834 (2019).
25. Eriksson, K. S., Sergeeva, O., Brown, R. E. & Haas, H. L. Orexin/hypocretin excites the histaminergic neurons of the tuberomammillary nucleus. *J. Neurosci.* **21**, 9273–9279 (2001).
26. Huang, Z. L. et al. Arousal effect of orexin A depends on activation of the histaminergic system. *Proc. Natl. Acad. Sci. USA* **98**, 9965–9970 (2001).
27. Anaclet, C. et al. Orexin/hypocretin and histamine: distinct roles in the control of wakefulness demonstrated using knock-out mouse models. *J. Neurosci.* **29**, 14423–14438 (2009).
28. Hara, J. et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron* **30**, 345–354 (2001).

Table

Table 1: Summary of key findings in the present study

Sleep parameter	Cisplatin Dark	Cisplatin Light	Cisplatin + JNJ777120 Dark	Cisplatin + JNJ777120 Light
Total sleep time	+ (Days 2, 3)	NS	NS	NS
Number of sleep episodes	+ (Days 1– 3)	+ (Days 1– 3)	High dose: – (Days 1–3)	Low/high dose: – (Day 3)
Mean sleep episode duration	– (Days 1– 3)	– (Days 1– 3)	High dose: + (Days 1, 3)	High dose: + (Day 3)

Figures

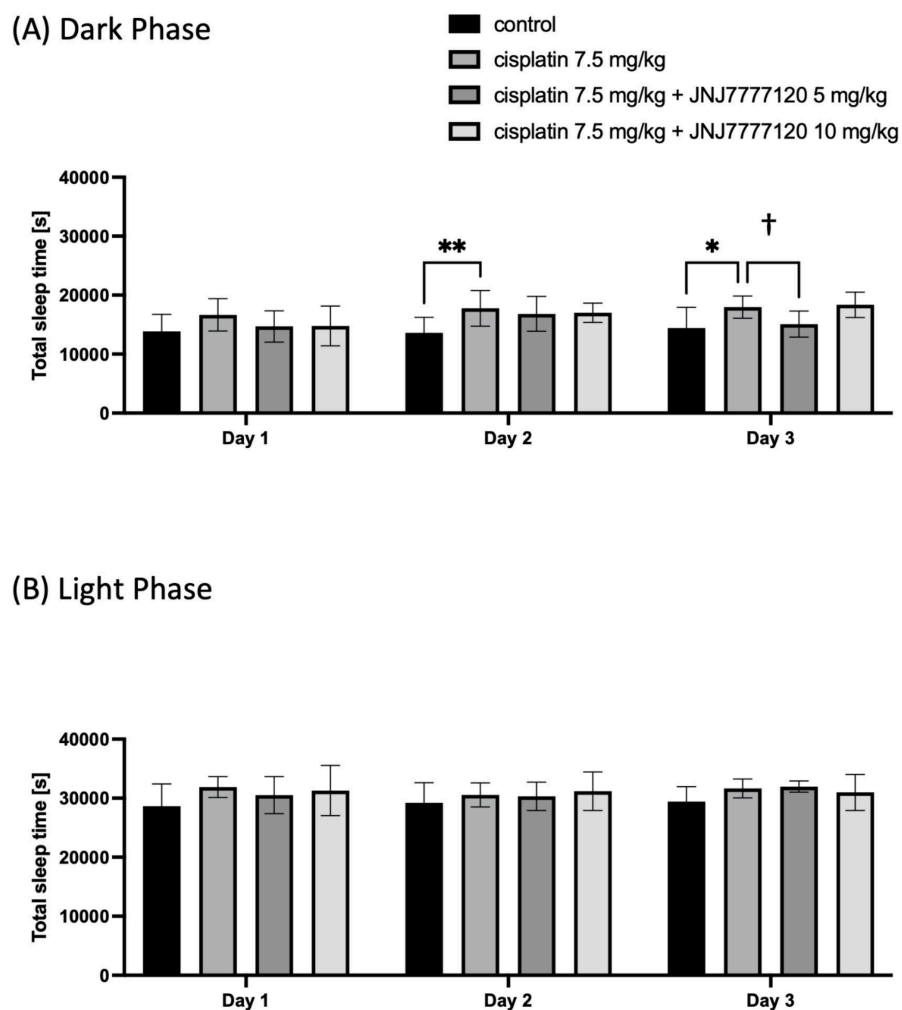


Figure 1

Figure 1

Effects of cisplatin and the histamine H4 receptor antagonist on total sleep time in mice.

Total sleep time was measured during dark (A) and light (B) phases on Days 1–3. Mice were treated with vehicle (control), cisplatin, cisplatin plus low dose (5 mg/kg) of JNJ7777120, or cisplatin plus high dose (10 mg/kg) of JNJ7777120. Data are expressed as the mean $\pm$ SD. Statistical analysis was performed

using two-way repeated-measures ANOVA with Geisser–Greenhouse correction, followed by Šídák's multiple-comparisons test. * $P < 0.05$ and ** $P < 0.01$ vs. control. † $P < 0.05$ vs. cisplatin alone. Group sizes were $n = 11$ for control and cisplatin groups and $n = 10$ for each of the low and high dose JNJ777120 groups.

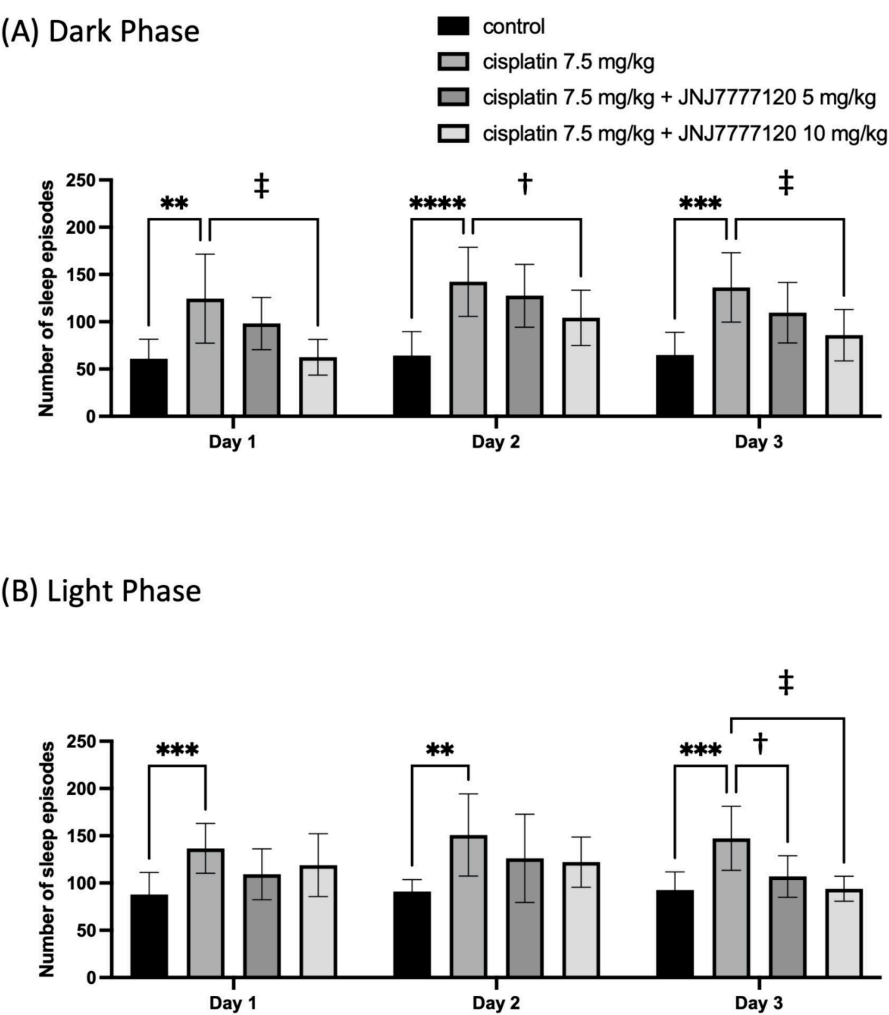


Figure 2

Figure 2

Effects of cisplatin and the histamine H4 receptor antagonist on the number of sleep episodes in mice.

The number of sleep episodes was determined during dark (A) and light (B) phases on Days 1–3. Mice were treated with vehicle (control), cisplatin, cisplatin plus low dose (5 mg/kg) of JNJ7777120, or cisplatin plus high dose (10 mg/kg) of JNJ7777120. Data are expressed as the mean $\pm$ SD. Statistical analysis was performed using two-way repeated-measures ANOVA with Geisser–Greenhouse correction, followed by Šídák's multiple-comparisons test. **P < 0.01, ***P < 0.001, and ****P < 0.0001 vs. control. † P < 0.05 and ‡ P < 0.01 vs. cisplatin alone. Group sizes were n = 11 for control and cisplatin groups and n = 10 for each of the low and high dose JNJ7777120 groups.

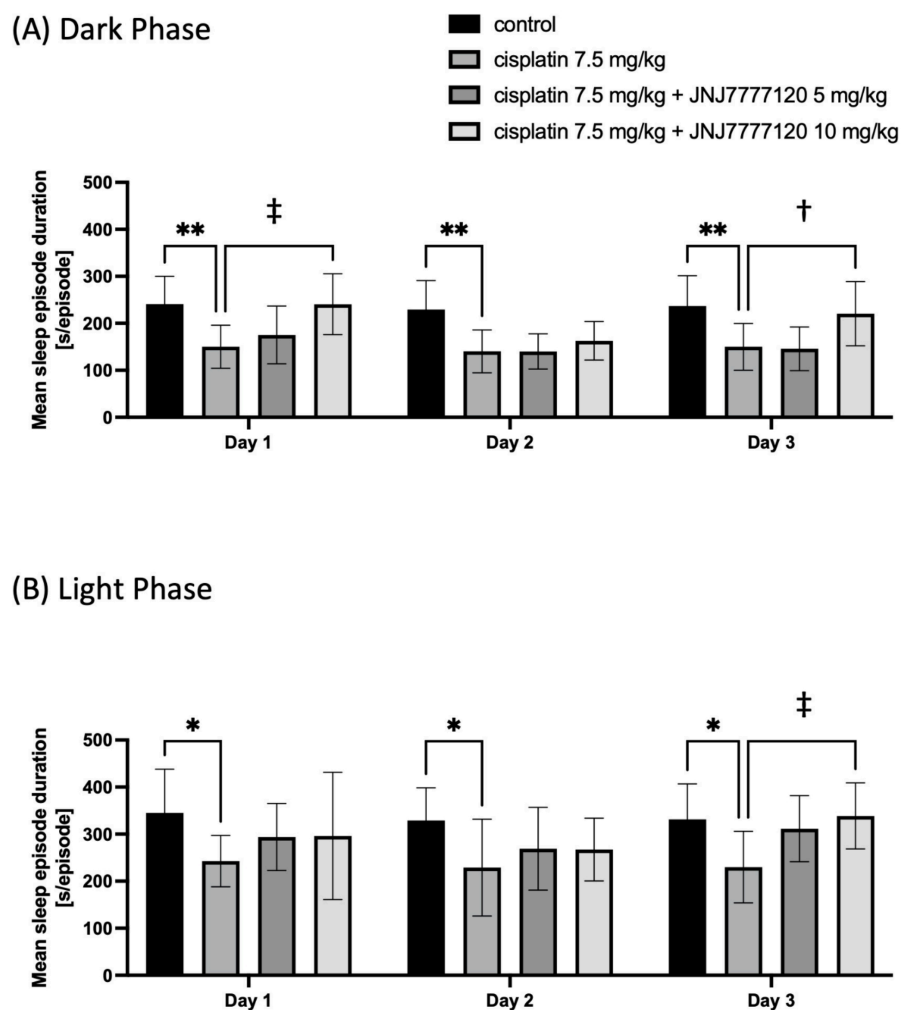


Figure 3

Figure 3

Effects of cisplatin and the histamine H4 receptor antagonist on mean sleep episode duration in mice.

Mean sleep episode duration was determined during dark (A) and light (B) phases on Days 1–3. Mice were treated with vehicle (control), cisplatin, cisplatin plus low dose (5 mg/kg) of JNJ7777120, or cisplatin plus high dose (10 mg/kg) of JNJ7777120. Data are expressed as the mean $\pm$ SD. Statistical

analysis was performed using two-way repeated-measures ANOVA with Geisser–Greenhouse correction, followed by Šídák's multiple-comparisons test. *P < 0.05 and **P < 0.01 vs. control. † P < 0.05 and ‡ P < 0.01 vs. cisplatin alone. Group sizes were n = 11 for control and cisplatin groups and n = 10 for each of the low and high dose of JNJ7777120 groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFigure.docx](#)