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ORIGINAL PAPER

Ethanol Induces Sedation and Hypnosis via Inhibiting Histamine Release in Mice

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Abstract

Ethanol is one of the most highly abused psychoactive compounds worldwide and induces sedation and hypnosis. The histaminergic system is involved in the regulation of sleep/wake function and is a crucial player in promoting wakefulness. To explore the role and mechanism of the histaminergic system in ethanol-induced sedation and hypnosis, we recorded locomotor activity (LMA) and electroencephalography (EEG)/electromyography (EMG) in mice using an infrared ray passive sensor recording system and an EEG/EMG recording system, respectively, after administration of ethanol. In vivo microdialysis coupled with high performance liquid chromatography and fluorometry technology were used to detect histamine release in the mouse frontal cortex (FrCx). The results revealed that ethanol significantly suppressed LMA of histamine receptor 1 (H_1R)-knockout (KO) and wild-type (WT) mice in the range of 1.5–2.5 g/kg, but suppression was remarkably stronger in WT mice than in H_1R-KO mice. At 2.0 and 2.5 g/kg, ethanol remarkably increased non-rapid eye movement sleep and decreased wakefulness, respectively. Neurochemistry experimental data indicated that ethanol inhibited histamine release in the FrCx in a dose-dependent manner. These findings suggest that ethanol induces sedation and hypnosis via inhibiting histamine release in mice.

Keywords Ethanol · Histamine · Sedation/hypnosis · Frontal cortex

Introduction

Ethanol (alcohol) is one of the most highly abused psychoactive compounds worldwide [1]. It produces extensive effects on the central nervous system (CNS) [2], for example, a variety of studies have documented that acute ethanol treatment induces sedation and hypnosis. In rodents, irrespective of the time of administration, acute ethanol treatment also reduces sleep onset latency and increases non-rapid eye movement (NREM) sleep [3–7]. Local bilateral infusion of ethanol (0.047, 0.24, and 0.47 μmol) into the preoptic region dose-dependently increases NREM sleep [8]. In healthy non-alcoholics, acute ethanol intake reduces the time to fall asleep (sleep onset latency) and consolidates and enhances the quality (delta power) and quantity of NREM sleep during the first half of the night [6]. In alcoholics, those sleep impairments are so severe that they are the primary predictors of relapse in recovering alcoholics [9, 10]. Thus, it is of paramount importance to identify the mechanism underlying the effects of ethanol on sedation and hypnosis.

Previous findings implicated the GABA system as playing a role in modulating the sedation/hypnosis of ethanol [11–14]. Fang et al. found that ethanol dose-dependently increased NREM sleep in mice, which was related to the adenosinergic system with the A_{2A} receptor, one of the receptors for the hypnotic effects of ethanol [7]. More recently, increasing attention has been paid to the effect of ethanol on the "excitatory" behaviors of mice that are altered by histamine in the brain. For example,

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pretreatment with immepip, a histamine H_3 receptor (H_3R) agonist, diminishes ethanol-induced locomotor activity (LMA) and increases the motor-impairing effects of ethanol on a balance beam, while the H_3R antagonist ciproxifan inhibits ethanol-evoked conditioned place preference (CPP) in mice [15]. Histamine is required for H_3R-mediated inhibition of alcohol-CPP, and the brain histaminergic system exerts an inhibitory role in alcohol reward in mice [16]. H_3R is an autoreceptor in presynaptic histaminergic neurons that controls histamine turnover by feedback inhibition of histamine synthesis and release [17]. Moreover, pretreatment with histamine or the histamine precursor L-histidine attenuates the acute anxiolytic-like effect of ethanol on the elevated plus maze in mice [18], although insufficient intake of histidine reduced the brain histamine content, leading to anxiety-like behaviors in mice [19]. These findings indicate that ethanol may alter locomotor activity, motor balance, CPP, rewarding, anxiety, etc. "excitatory behaviors" via influencing histamine in the brain.

Histamine is an important biological active neurotransmitter secreted by histaminergic neurons that originate from the tuberomammillary nucleus (TMN) of the posterior hypothalamus and project efferent nerve fibers to almost all parts of the brain in mammals [20, 21]. It is commonly accepted that histamine is involved in the regulation of sleep–wake function, especially as a crucial player in promoting wakefulness through histamine H_1R and/or H_3R [22–27] and spontaneous LMA [28, 29]. Some evidences also indicate that brain-derived histamine plays an important role in the sedative effects of ethanol. Lintunen et al. reported that rats genetically selected for their high tolerance to the ataxic effects of ethanol exhibit higher levels of brain histamine, along with a higher density of histamine-immunoreactive nerve fibers [30]. In addition, pretreatment with the histamine precursor L-histidine significantly reduces ethanol-induced sedation [31], and ethanol itself also influences brain histamine contents, i.e. acute treatment of guinea-pigs with ethanol decreased histamine content in the hypothalamus, cerebral cortex, etc. regions and in the whole brain [32]. Based on these findings, we hypothesized that ethanol may induce sedation and hypnosis by inhibiting the histaminergic transmission and histamine levels in the brain.

In the present study, we investigated the effect of the histaminergic system on ethanol-induced sedation and hypnosis in mice by recording LMA, electroencephalography (EEG), and electromyography (EMG). In vivo microdialysis coupled with high-performance liquid chromatography (HPLC) and fluorometry was used to detect changes of histamine level induced by ethanol in mice to explore the mechanism underlying ethanol-induced sedation and hypnosis.

Materials and Methods

Animals

Male inbred (C57BL/6J strain) WT and H_1R-knockout (KO) mice [33] (11–13 weeks old, 22–26 g body weight) were used in these experiments. All animals were housed at a constant temperature (24 ± 0.5 °C) with relative humidity (60 ± 2%) and an automatically controlled 12 h:12 h light/dark cycle (lights on at 07:00, illumination intensity ≈ 100 lx) [34]. Animals had ad libitum access to food and water. The experimental protocols were approved by the Medical Experimental Animal Administrative Committee of Wannan Medical College.

Drugs and Chemicals

Ethanol, GABA, and histamine were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). All other chemicals were of analytical grade.

LMA Recordings

LMA for an individual H_1R-KO or WT mouse was monitored using a passive infrared sensor (Biotex, Kyoto, Japan) placed 17.5 cm above the floor of the recording cage (28 cm × 16.5 cm × 13 cm) as previously reported [35]. After the animals were placed into cages for a 3-day habituation period, their LMA were recorded for 24 h as the data under physiological conditions. Then, animals were injected (i.p.) with vehicle (saline, 0.9% NaCl) or different doses of ethanol at 20:00 (operating under the red light of approximately 10 lx illumination intensity) [34], and their LMA was recorded consecutively for 24 h after the injection. During monitoring, mice had free access to food and water.

Polygraphic Recordings and Vigilance State Analysis

Under chloral hydrate anesthesia (360 mg/kg, i.p.), H_1R-WT mice were simultaneously implanted with electrodes for polysomnographic recordings using EEG and EMG. Implants consisted of two stainless-steel screws (1 mm diameter) inserted through the skull of the cortex (anteroposterior, + 1.0 mm; left–right, − 1.5 mm from bregma) according to the atlas of Paxinos and Franklin [36] and served as EEG electrodes. Two insulated stainless-steel, Teflon-coated wires were bilaterally placed into both trapezius muscles to

serve as EMG electrodes. All electrodes were attached to a microconnector and fixed to the skull with dental cement [37].

EEG and EMG recordings were performed by means of a slip ring, designed so that the behavioral movement of the mice would not be restricted [38]. After a 10-day recovery period, mice were housed individually in transparent barrels and habituated to the recording cable for 3–4 days before polygraphic recording. Sleep–wake states were monitored for 48 h, comprising baseline and experimental days. Baseline recordings were taken in each animal for 24 h to serve as the control. Then, animals were injected (i.p.) with different doses of ethanol at 20:00 (operating under the red light of 10 lx illumination intensity), and sleep–wake states were consecutively recorded for 24 h after the injection. During monitoring, mice had free access to food and water.

Cortical EEG and EMG signals were amplified and filtered (EEG, 0.5–30 Hz; EMG, 20–200 Hz) and then digitized at a sampling rate of 128 Hz and recorded using SleepSign (Kissei Comtec, Nagano, Japan) as described previously [23]. When complete, polygraphic recordings were automatically scored off-line by 4 s epochs as wakefulness, rapid eye movement (REM), or NREM sleep by SleepSign according to standard criteria [39], where (1) represents wakefulness (high EMG and low EEG amplitude and high theta activity concomitant with the highest EMG values) (2) represents NREM sleep (low EMG and high EEG amplitude, high delta activity), and (3) represents REM sleep (low EMG and low EEG amplitude, high theta activity).

Dialysate Collection

H_1R-WT mice were anesthetized using urethane (1.8 g/kg, i.p.), and a microdialysis probe (CMA/12, membrane length of 2 mm; CMA/Microdialysis, Stockholm) was stereotaxically inserted into the FrCx (anteroposterior, + 1.8 mm; right side, − 0.8 mm from bregma; depth, 2.3 mm beneath the surface of the skull) according to the atlas of Paxinos and Franklin [36] to collect dialysates to measure extracellular histamine (Fig. 1). The microdialysis probe was perfused with artificial cerebrospinal fluid (aCSF; composition [mM]: 140 NaCl, 3 KCl, 1 $MgCl_2$, 1.3 $CaCl_2$, 2 Na_2HPO_4, and 0.2 NaH_2PO_4, pH 7.4) at a flow rate of 2 µl/min. Two hours after insertion of the probe, dialysates were collected continuously at 20-min intervals (40 µl each) for 1 h before saline or ethanol injection (i.p.) and until 3 h for detecting histamine since the pre-experimental result showed that at the end of 3-h after ethanol administration, the decreased histamine level induced by ethanol (2.5 g/kg) in FrCx of mice was gradually returned to the basal level. Dialysates were kept at − 80 °C until assayed by HPLC-fluorometry for histamine.

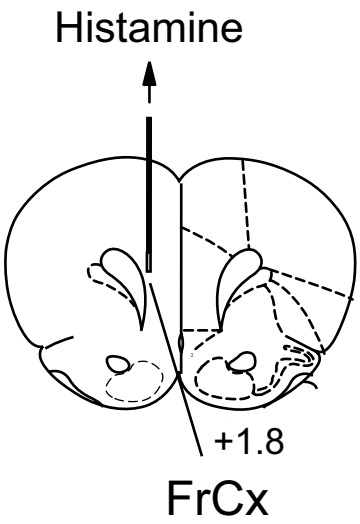

Fig. 1 Schematic representation of implantation sites for microdialysis probes. Probe sites in the frontal cortex (FrCx) of mice are shown

Dialysate Histamine Measurement

Histamine levels in dialysates were assessed by HPLC-fluorometry [22, 40]. Briefly, 35 µl of dialysate sample was injected into a column packed with a cation exchanger, TSK gel SP2SW (Ø 6 mm × 150 mm; Tosoh, Tokyo, Japan), and eluted with 0.25 M KH_2PO_4 at a flow rate of 0.9 ml/min. Histamine was post-labeled with 0.1% *o*-phthalaldehyde under alkaline conditions and detected fluorometrically in an F1080 fluorometer (Hitachi, Tokyo, Japan) using excitation and emission wavelengths of 360 nm and 450 nm, respectively.

Chromatograms for histamine were recorded and analyzed using Millennium32 Chromatography Manager Software (Waters, Milford, MA).

Statistical Analysis

All data are expressed as means ± SEMs. For in vivo microdialysis studies, the mean values of histamine found from three dialysate samples before administration of drugs were defined as the basal release, and subsequent fractions are expressed as percentages of this value. For LMA studies, the suppression rate of LMA was defined as a percentage: $(LMA_{saline} - LMA_{alcohol}) / LMA_{saline} \times 100\%$ (where $LMA_{alcohol}$ is the 4-h accumulated count of LMA after injection of different concentrations of alcohol, and LMA_{saline} is the 4-h accumulated count of LMA after injection of saline). Statistical analyses were performed using analysis of variance (ANOVA) followed by post hoc Newman-Keuls test or two-tailed Student's *t*-test. In all cases, $P < 0.05$ was interpreted as statistically significant.

Results

Under Physiological Conditions, LMA Exhibits Nocturnal Rhythm Changes in Both H_1R-KO and WT mice

Under physiological conditions, as shown in Fig. 2, WT mice exhibited a clear nocturnal rhythm of LMA being high during the dark period and low during the light period. Accumulated LMA during the dark period was approximately 4.3 times that in the light period (Fig. 2a). Similarly, H_1R-KO mice also exhibited the same LMA rhythm as WT mice in which accumulated LMA during the dark period was approximately 4.2 times that in the light period (Fig. 2b). There were no significant differences in LMA either during the dark period or during the light period between the two genotypes of mice [P = 0.4360 and P = 0.9115, respectively] (Fig. 2c).

Ethanol Suppresses LMA in Both H_1R-KO and WT Mice but Exerts Stronger Effects in WT Mice

At a dose of 2.0 g/kg, ethanol significantly suppressed LMA of both genotypes of mice compared with saline. However, the suppression was significantly stronger in WT mice than in H_1R-KO mice. In WT mice, the suppression was sustained for approximately 4 h [all P values < 0.05] (Fig. 3a), whereas it only lasted 1 h in H_1R-KO mice [P = 0.0009] (Fig. 3b). For comparison of the differences in ethanol dose on LMA, we calculated the 4-h accumulated count of LMA after ethanol administration. The results revealed that ethanol dose-dependently suppressed LMA in both H_1R-KO [F(3,23) = 9.982, P = 0.000; Q-value for 2.5 g/kg or 1.5 g/kg versus saline = 7.358 or 5.343; corresponding P-values all < 0.01] and WT mice [F(3,23) = 15.890, P = 0.000; Q-value for 2.5 g/kg or 1.5 g/kg versus saline = 9.053 or 5.138; corresponding P-values all < 0.01] (Fig. 3c) but that the suppression was stronger in WT mice than in H_1R-KO mice [for 2.0 g/kg, P = 0.045; for 2.5 g/kg, P = 0.01] (Fig. 3c). In WT mice, suppression rates of 4-h LMA after ethanol administration were 32%, 68%, and 94% at doses of 1.5, 2.0, and 2.5 g/kg ethanol, respectively. In contrast, in H_1R-KO mice, these rates were 23%, 45%, and 77%, respectively [for 2.0 g/kg, P = 0.0083; for 2.5 g/kg, P = 0.002] (Fig. 3d).

Ethanol Induces Hypnotic Effects in Mice

To determine whether ethanol exerted a hypnotic effect in mice during the dark phase, ethanol doses of 1.5, 2.0, or 2.5 g/kg were administered at 20:00 on the day of the experiment. Time course changes revealed that 2.5 g/kg ethanol significantly increased NREM sleep while decreasing wakefulness and REM sleep in mice compared with the saline group [P < 0.05] (Fig. 4a). Ethanol increased hourly NREM sleep times by 52%,

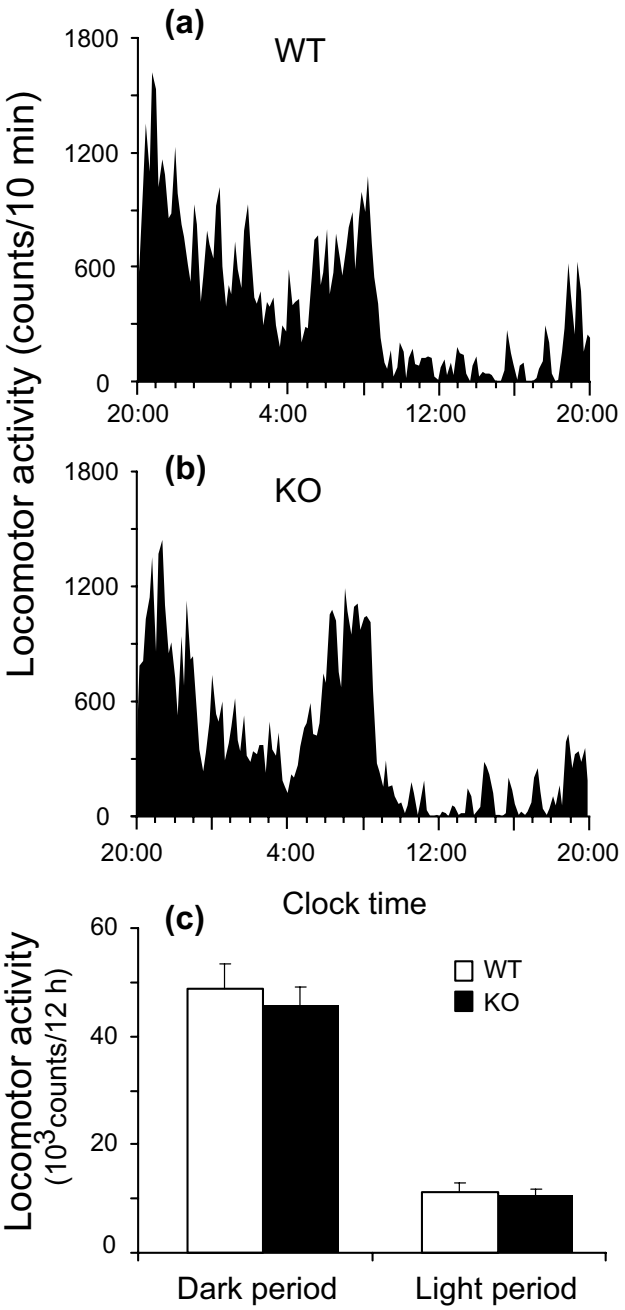

Fig. 2 Locomotor activity (LMA) of H_1R-KO and wild-type (WT) mice under physiological conditions. Ten-minute LMA of H_1R-WT (**a**) and H_1R-KO (**b**) mice and comparison of LMA during both dark and light periods between the two genotypes (**c**) are shown. Values represent the mean ± SEMs (n = 7–8). Two-tailed Student's *t*-test was used to analyze statistical significance; no difference was observed between H_1R-KO and WT mice during either the dark or the light period

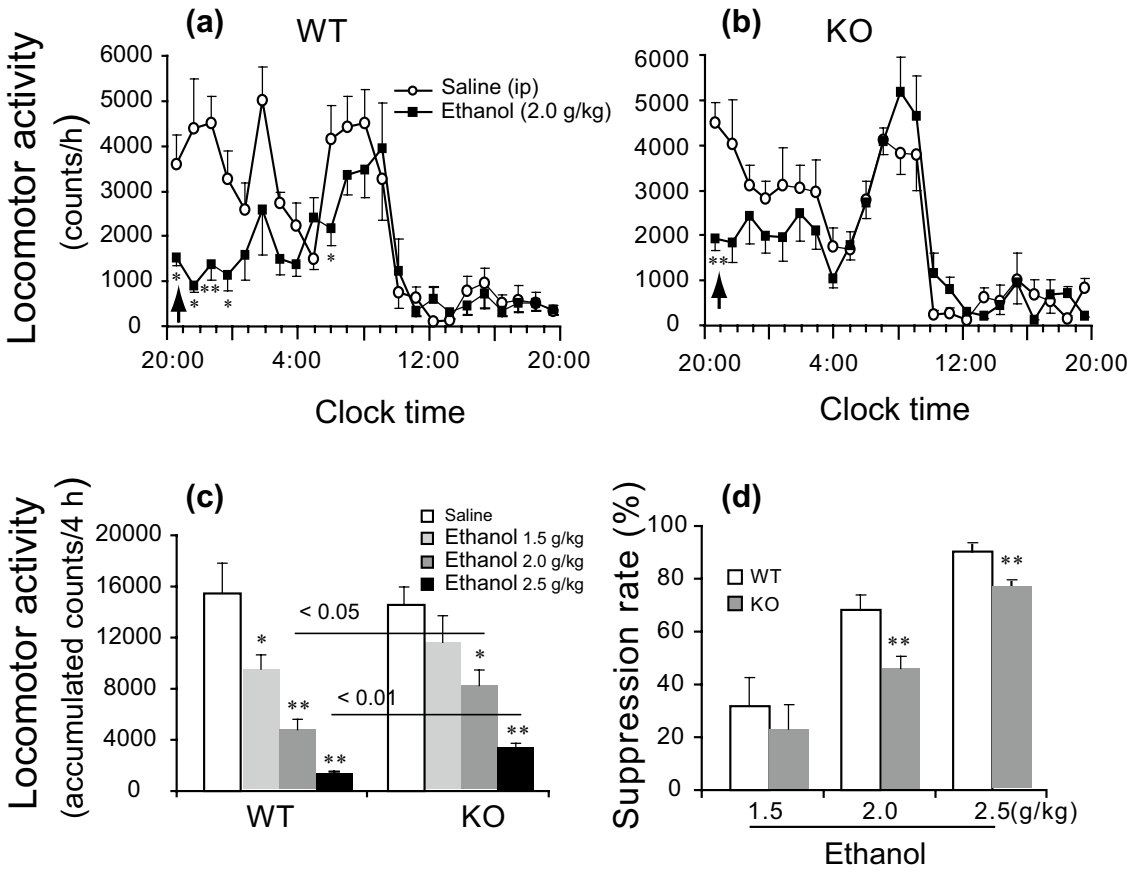

Fig. 3 Effects of ethanol on locomotor activity (LMA) in H_1R-KO and WT mice. Time-courses (**a**, **b**), four-hour accumulated amounts (**c**) and 4-h suppression rates (**d**) of LMA after administration of ethanol or saline are shown. Each circle or square represents hourly mean counts of LMA. The solid arrow indicates the time point for i.p. Injection. Values represent the mean ± SEMs (n = 6–7). ANOVA followed by post hoc Newman-Keuls test or two-tail Student's *t*-test was used to analyze statistical significance; *P < 0.05, **P < 0.01 versus saline group, 1.5 g/kg ethanol group, or WT mice

39%, 25%, 23%, 12%, and 59% relative to the saline group during the first six hours after administration, respectively.

The total amounts of time spent in NREM, REM sleep, and wakefulness during the 6 h following treatment with ethanol in mice are summarized in Fig. 4b. At 2.0 and 2.5 g/kg, ethanol significantly increased NREM sleep by 25% and 26% [F(3,20) = 3.619, P = 0.031; Q-value for 2.0 g/kg or 2.5 g/kg versus saline = 3.711 or 4.113, corresponding P-values all < 0.05], while decreasing wakefulness by 10% and 15% [F(3,20) = 4.251, P = 0.021; Q-value for 2.5 g/kg versus saline = 3.428, P = 0.029] and REM sleep [F(3,20) = 3.851, P = 0.024; Q-value for 2.5 g/kg versus saline = 3.517, P = 0.021], respectively. These results indicate that ethanol increases NREM sleep in mice.

Ethanol Inhibits Histamine Release in the FrCx of Anesthetized Mice

As shown in Fig. 5a, 2.0 g/kg ethanol inhibited histamine release in the FrCx of mice to 62% and 50% of basal release at 40 and 60 min, respectively. Decreased histamine levels gradually returned to basal levels. When 2.5 g/kg ethanol was given, histamine release was decreased more rapidly, reaching its minimal level of 26% of basal release 40 min after dosing [F(3,44) = 8.479, P = 0.000; for 1.5 g/kg, 2.0 g/kg or 2.5 g/kg versus saline, P-values all < 0.05; for 2.5 g/kg versus 1.5 g/kg, P-values all < 0.05] (Fig. 5a).

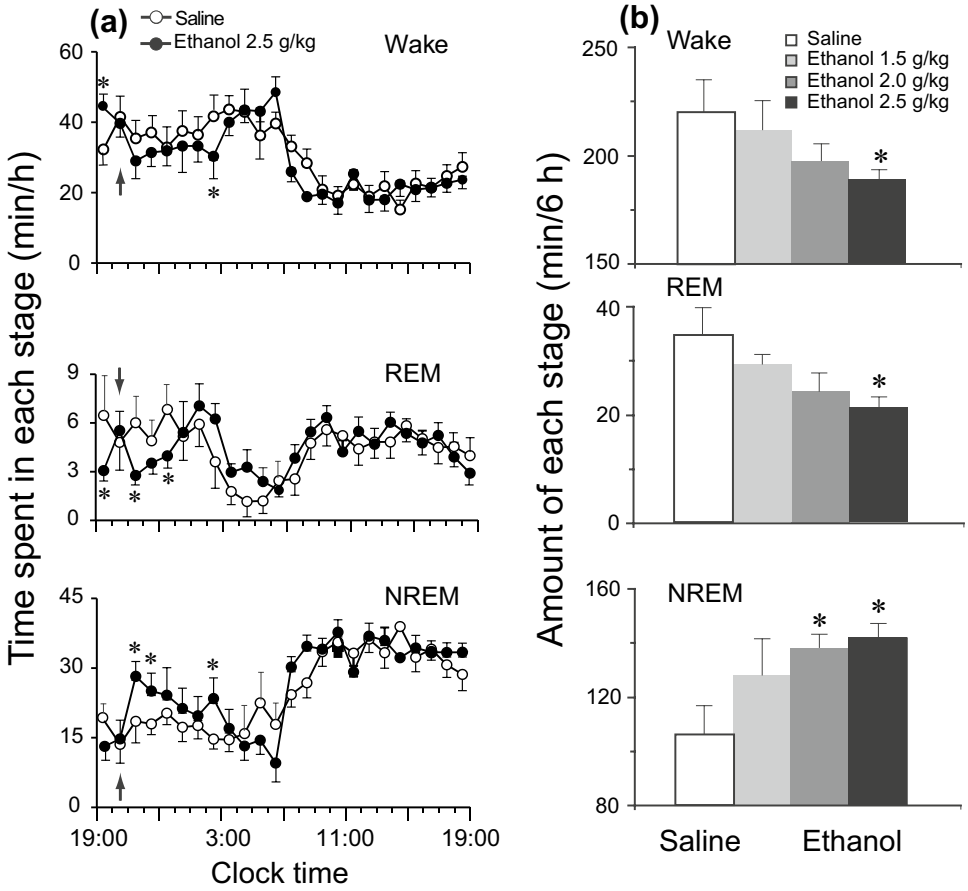

Fig. 4 Effects of ethanol on sleep and wakefulness in mice. Time-courses (**a**), six-hour accumulated amounts (**b**) of non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep and wakefulness after administration of ethanol or saline are shown. Each circle represents hourly mean values of each stage. The solid arrow indicates the time point for i.p. injection. Values represent the mean ± SEMs (n = 6). ANOVA followed by post hoc Newman-Keuls test or two-tailed Student's *t*-test was used to analyze statistical significance; *P < 0.05 versus saline group or 1.5 g/kg ethanol group

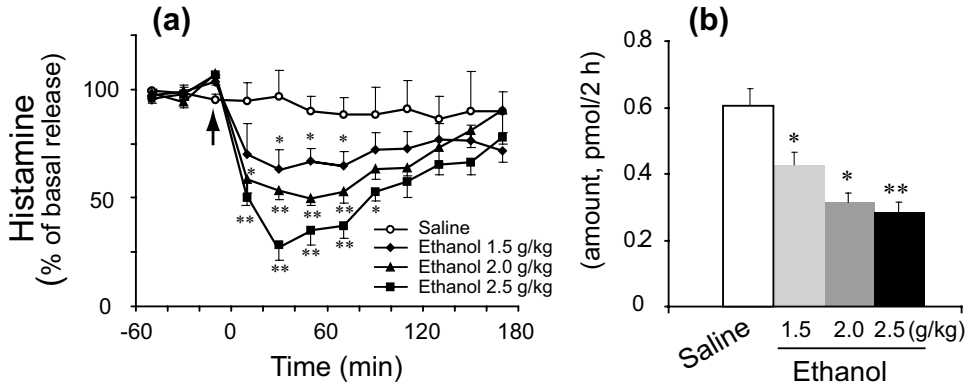

Fig. 5 Effects of ethanol on histamine release in the frontal cortex (FrCx) of anesthetized mice. Time-courses (**a**) and two-hour accumulated amounts (**b**) of histamine released after administration of ethanol or saline are shown. Each circle, square, or triangle represents the mean levels of histamine released per 20 min. The solid arrow indicates the time point for i.p. Injection. Values represent the mean ± SEMs (n = 4–5). ANOVA followed by post hoc Newman-Keuls test was used to analyze statistical significance; *P < 0.05, **P < 0.01 versus saline group or 1.5 g/kg ethanol group

For exploring the dose–effect relationship between ethanol and ethanol-induced inhibition of histamine release, we calculated the total level of histamine released over a 2-h period following ethanol administration. As shown in Fig. 5b, total levels of histamine released were 0.43 ± 0.04, 0.31 ± 0.03 and 0.28 ± 0.03 pmol/2 h at doses of 1.5, 2.0 and 2.5 g/kg ethanol, respectively. Ethanol given at a dose of 2.0 or 2.5 g/kg resulted in histamine release being significantly higher compared to the 1.5 g/kg dose [F(3,13) = 32.643, P = 0.000; Q-value for 2.0 g/kg or 2.5 g/kg versus 1.5 g/

kg = 3.628 or 4.355, the corresponding P-values all < 0.05] (Fig. 5b), indicating that ethanol inhibits histamine release in a dose-dependent manner.

Discussion

In the present study, we demonstrated that ethanol induces sedative and hypnotic effects, while ethanol-induced inhibition of histamine release was observed in the FrCx. These findings suggest that the sedative and hypnotic effects of ethanol result from inhibition of the histaminergic system.

Histaminergic neurons located in the TMN are critical in regulating motion and wakefulness. Histamine exerts its effects through four receptors (H_1, H_2, H_3 and H_4), which are widely distributed throughout the brain [20, 25]. Previous studies have found that the histaminergic system plays a major role in the regulation of spontaneous LMA which is a classic index for sedation. During wakefulness, extracellular histamine levels in the anterior hypothalamic area and spontaneous LMA are positively correlated in rats [28]. Furthermore, histaminergic neurons are active only during wakefulness, and their activity is related to a high level of vigilance in mice. Conversely, histaminergic neurons cease firing during the drowsy state, which is characterized by low vigilance levels [29]. We report for the first time that the inhibitory effect of ethanol on spontaneous LMA in H_1R-KO mice was significantly weaker than in WT mice, indicating that the histaminergic system may play an important role in the ethanol-induced sedative effect.

Here, we provided explicit results illustrating that 2.5 g/kg ethanol administration induced sustained increases in NREM sleep for more than 6 h in mice. This phenomenon is consistent with previous studies. For example, a clinical study demonstrated that alcohol-increased SWS (slow wave sleep) during the first part of the night is more clearly associated with a high alcohol dose in healthy young adults [41]. In addition, ethanol producing the effects of drowsiness and hypnosis has also been reported in rodents [5]. Histamine, an arousal neurotransmitter, has been proven to regulate cortical neurons by promoting cortical wakefulness, likely either through direct cortical projections or by tonic control over the sleep-generating mechanisms in the preoptic hypothalamus of cats [42–44]. Moreover, histamine concentration is highly positively correlated with active wakefulness in mice [45, 46], in which the histamine release was 3.8 times higher during wake episodes than during sleep episodes [45]. These results suggest that the concentration change of cortical histamine plays a role in the regulation of sleep–wake behavior. On the other hand, it has been verified that ethanol may change brain histamine levels by affecting the histamine metabolism and release processes in the histaminergic pathway of the brain. Subramanian et al. reported that depolarisation-induced release of histamine was inhibited by ethanol in the hypothalamus, thalamus and cortex of rats, and also ethanol decreased histidine decarboxylase (HDC) activity in the brain [47]. Rawat found that maternal ethanol consumption during pregnancy results in an increase in the cerebral histamine levels of the fetus, and the brain histamine levels are highest towards latter part of the pregnancy and lowest in the adult brains, whereas the brain HDC activity is lowest in the fetal brains and highest in the adult brains [48]. Moreover, Itoh et al. found that a large dose of ethanol apparently decreases histamine turnover in the mouse hypothalamus to influence brain histamine levels [49]. And further different doses of ethanol may cause different effects on histamine concentration and HDC activity in different brain regions, which may be involved two separate dose-dependent neurochemical effects of ethanol [50]. In present study, we used an in vivo microdialysis method to investigate the relationship between histamine release and ethanol, and demonstrated that ethanol decreased histamine levels in the FrCx. Taken together, we speculate that ethanol decreases the excitatory effect of histaminergic systems in the cortex, leading to sedation and hypnosis in mice.

As to how ethanol inhibits histamine release in the FrCx, Sun et al. reported that ethanol may inhibit the excitability of histaminergic neurons in mouse TMN slices via potentiating GABAergic transmission onto the neurons at both pre- and postsynaptic sites [14]. We found that CGS21680, an adenosine A_{2A} receptor agonist, induces sleep by inhibiting the histaminergic system through increasing GABA release in the TMN in rats [22]. And some previous studies showed that ethanol increased GABA release in different brain regions. For example, Smith et al. found that 0.5 and 1.0 g/kg ethanol exhibited dose-related increases in GABA in the nucleus accumbens and dorsal striatum of rats [51]. Chronic ethanol-treated rats exhibited an approximately four-fold increase in baseline GABA dialysate content in the central nucleus of the amygdala (CeA) compared with naive rats. Moreover, in vivo administration of ethanol (0.1, 0.3, and 1.0 mM) produced a dose-dependent increase in GABA release in CeA dialysate in both chronic ethanol-treated and naive rats [52]. Taken together, we speculate that ethanol may increase GABA release in the TMN to inhibit histamine release in the FrCx in mice.

Comprehensively analyzing these findings, it is logical that systemically administration of ethanol induces effects of sedation and hypnosis through increasing GABA release to potentiate GABAergic transmission onto neurons to suppress the TMN, a wakefulness center.

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Author Contributions ZYH and ZLH designed the experiments and guided the writing of this article. ZQM, WSW, TXW and WX were responsible for performing experiments and writing the manuscript. WMQ contributed to acquire and analyze the data. Authors included in this article agreed with the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest.

References

1. Pesta DH, Angadi SS, Burtscher M, Roberts CK (2013) The effects of caffeine, nicotine, ethanol, and tetrahydrocannabinol on exercise performance. Nutr Metab 10:71
2. Ferreira MP, Willoughby D (2008) Alcohol consumption: the good, the bad, and the indifferent. Appl Physiol Nutr Metab 33:12–20
3. Hattan DG, Eacho PI (1978) Relationship of ethanol blood level to REM and non-REM sleep time and distribution in the rat. Life Sci 22:839–846
4. Hill SY, Reyes RB (1978) Effects of chronic and acute ethanol administration on sleep in laboratory rats. J Stud Alcohol 39:47–55
5. Kubota T, De A, Brown RA, Simasko SM, Krueger JM (2002) Diurnal effects of acute and chronic administration of ethanol on sleep in rats. Alcohol Clin Exp Res 26:1153–1161
6. Thakkar MM, Sharma R, Sahota P (2015) Alcohol disrupts sleep homeostasis. Alcohol 49:299–310
7. Fang T, Dong H, Xu XH, Yuan XS, Chen ZK, Chen JF, Qu WM, Huang ZL (2017) Adenosine A2A receptor mediates hypnotic effects of ethanol in mice. Sci Rep 7:12678
8. Ticho SR, Stojanovic M, Lekovic G, Radulovacki M (1992) Effects of ethanol injection to the preoptic area on sleep and temperature in rats. Alcohol 9:275–278
9. Brower KJ (2003) Insomnia, alcoholism and relapse. Sleep Med Rev 7:523–539
10. Brower KJ, Perron BE (2010) Prevalence and correlates of withdrawal-related insomnia among adults with alcohol dependence: results from a national survey. Am J Addict 19:238–244
11. Martin LJ, Zurek AA, Bonin RP, Oh GH, Kim JH, Mount HT, Orser BA (2011) The sedative but not the memory-blocking properties of ethanol are modulated by alpha5-subunit-containing gamma-aminobutyric acid type A receptors. Behav Brain Res 217:379–385
12. Blednov YA, Benavidez JM, Black M, Leiter CR, Osterndorff-Kahanek E, Johnson D, Borghese CM, Hanrahan JR, Johnston GA, Chebib M et al (2014) GABAA receptors containing rho1 subunits contribute to in vivo effects of ethanol in mice. PLoS ONE 9:e85525
13. Santerre JL, Gigante ED, Landin JD, Werner DF (2014) Molecular and behavioral characterization of adolescent protein kinase C following high dose ethanol exposure. Psychopharmacology 231:1809–1820
14. Sun Y, Jiang SY, Ni J, Luo YJ, Chen CR, Hong ZY, Yanagawa Y, Qu WM, Wang L, Huang ZL (2016) Ethanol inhibits histaminergic neurons in mouse tuberomammillary nucleus slices via potentiating GABAergic transmission onto the neurons at both pre- and postsynaptic sites. Acta Pharmacol Sin 37:1325–1336
15. Nuutinen S, Vanhanen J, Pigni MC, Panula P (2011) Effects of histamine H3 receptor ligands on the rewarding, stimulant and motor-impairing effects of ethanol in DBA/2J mice. Neuropharmacology 60:1193–1199
16. Vanhanen J, Nuutinen S, Lintunen M, Maki T, Ramo J, Karlstedt K, Panula P (2013) Histamine is required for H(3) receptor-mediated alcohol reward inhibition, but not for alcohol consumption or stimulation. Br J Pharmacol 170:177–187
17. West RE Jr, Zweig A, Shih NY, Siegel MI, Egan RW, Clark MA (1990) Identification of two H3-histamine receptor subtypes. Mol Pharmacol 38:610–613
18. Verma L, Jain NS (2016) Central histaminergic transmission modulates the ethanol induced anxiolysis in mice. Behav Brain Res 313:38–52
19. Yoshikawa T, Nakamura T, Shibakusa T, Sugita M, Naganuma F, Iida T, Miura Y, Mohsen A, Harada R, Yanai K (2014) Insufficient intake of L-histidine reduces brain histamine and causes anxiety-like behaviors in male mice. J Nutr 144:1637–1641
20. Haas H, Panula P (2003) The role of histamine and the tuberomamillary nucleus in the nervous system. Nat Rev Neurosci 4:121–130
21. Haas HL, Sergeeva OA, Selbach O (2008) Histamine in the nervous system. Physiol Rev 88:1183–1241
22. Hong ZY, Huang ZL, Qu WM, Eguchi N, Urade Y, Hayaishi O (2005) An adenosine A receptor agonist induces sleep by increasing GABA release in the tuberomammillary nucleus to inhibit histaminergic systems in rats. J Neurochem 92:1542–1549
23. Huang ZL, Mochizuki T, Qu WM, Hong ZY, Watanabe T, Urade Y, Hayaishi O (2006) Altered sleep-wake characteristics and lack of arousal response to H3 receptor antagonist in histamine H1 receptor knockout mice. Proc Natl Acad Sci USA 103:4687–4692
24. Oishi Y, Huang ZL, Fredholm BB, Urade Y, Hayaishi O (2008) Adenosine in the tuberomammillary nucleus inhibits the histaminergic system via A1 receptors and promotes non-rapid eye movement sleep. Proc Natl Acad Sci USA 105:19992–19997
25. Tokunaga S, Tsutsui R, Obara Y, Ishida T, Kamei C (2009) Effects of histamine H1-antagonists on sleep-awake state in rats placed on a grid suspended over water or on sawdust. Biol Pharm Bull 32:51–54
26. Liu TY, Hong ZY, Qu WM, Huang ZL (2011) Advances in the study of histaminergic systems and sleep-wake regulation. Yao Xue Xue Bao 46:247–252
27. Huang ZL, Zhang Z, Qu WM (2014) Roles of adenosine and its receptors in sleep-wake regulation. Int Rev Neurobiol 119:349–371
28. Mochizuki T, Yamatodani A, Okakura K, Horii A, Inagaki N, Wada H (1992) Circadian rhythm of histamine release from the hypothalamus of freely moving rats. Physiol Behav 51:391–394
29. Takahashi K, Lin JS, Sakai K (2006) Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse. J Neurosci 26:10292–10298
30. Lintunen M, Raatesalmi K, Sallmen T, Anichtchik O, Karlstedt K, Kaslin J, Kiianmaa K, Korpi ER, Panula P (2002) Low brain histamine content affects ethanol-induced motor impairment. Neurobiol Disord 9:94–105
31. Didone V, Quoilin C, Nyssen L, Closon C, Tirelli E, Quertemont E (2013) Effects of L-histidine and histamine H3 receptor modulators on ethanol-induced sedation in mice. Behav Brain Res 238:113–118
32. Nowak JZ, Maslinski C (1984) Ethanol-induced changes of histamine content in guinea-pig brain. Pol J Pharmacol Pharm 36:647–651
33. Inoue I, Yanai K, Kitamura D, Taniuchi I, Kobayashi T, Niimura K, Watanabe T, Watanabe T (1996) Impaired locomotor activity and exploratory behavior in mice lacking histamine H1 receptors. Proc Natl Acad Sci USA 93:13316–13320
34. Zhang Z, Wang HJ, Wang DR, Qu WM, Huang ZL (2017) Red light at intensities above 10 lx alters sleep-wake behavior in mice. Light Sci Appl 6:e16231

35. Nakamura W, Yamazaki S, Nakamura TJ, Shirakawa T, Block GD, Takumi T (2008) In vivo monitoring of circadian timing in freely moving mice. Curr Biol 18:381–385
36. Paxinos G, Franklin KBJ (2001) The mouse brain in stereotaxic coordinates, 2nd edn. Academic Press, San Diego
37. Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y (2008) Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil. J Neurosci 28:8462–8469
38. Wang TX, Yin D, Guo W, Liu YY, Li YD, Qu WM, Han WJ, Hong ZY, Huang ZL (2015) Antinociceptive and hypnotic activities of pregabalin in a neuropathic pain-like model in mice. Pharmacol Biochem Behav 135:31–39
39. Tobler I, Deboer T, Fischer M (1997) Sleep and sleep regulation in normal and prion protein-deficient mice. J Neurosci 17:1869–1879
40. Yamatodani A, Fukuda H, Wada H, Iwaeda T, Watanabe T (1985) High-performance liquid chromatographic determination of plasma and brain histamine without previous purification of biological samples: cation-exchange chromatography coupled with post-column derivatization fluorometry. J Chromatogr 344:115–123
41. Arnedt JT, Rohsenow DJ, Almeida AB, Hunt SK, Gokhale M, Gottlieb DJ, Howland J (2011) Sleep following alcohol intoxication in healthy, young adults: effects of sex and family history of alcoholism. Alcohol Clin Exp Res 35:870–878
42. Lin JS, Hou Y, Sakai K, Jouvet M (1996) Histaminergic descending inputs to the mesopontine tegmentum and their role in the control of cortical activation and wakefulness in the cat. J Neurosci 16:1523–1537
43. Lin JS, Sakai K, Jouvet M (1994) Hypothalamo-preoptic histaminergic projections in sleep-wake control in the cat. Eur J Neurosci 6:618–625
44. Lin JS, Sakai K, Vanni-Mercier G, Arrang JM, Garbarg M, Schwartz JC, Jouvet M (1990) Involvement of histaminergic neurons in arousal mechanisms demonstrated with H3-receptor ligands in the cat. Brain Res 523:325–330
45. Chu M, Huang ZL, Qu WM, Eguchi N, Yao MH, Urade Y (2004) Extracellular histamine level in the frontal cortex is positively correlated with the amount of wakefulness in rats. Neurosci Res 49:417–420
46. Rozov SV, Zant JC, Karlstedt K, Porkka-Heiskanen T, Panula P (2014) Periodic properties of the histaminergic system of the mouse brain. Eur J Neurosci 39:218–228
47. Subramanian N, Schinzel W, Mitznegg P, Estler CJ (1980) Influence of ethanol on histamine metabolism and release in the rat brain. II. Regions of the histaminergic pathway. Pharmacology 20:42–45
48. Rawat AK (1980) Development of histaminergic pathways in brain as influenced by maternal alcoholism. Res Commun Chem Pathol Pharmacol 27:91–103
49. Itoh Y, Nishibori M, Oishi R, Saeki K (1985) Changes in histamine metabolism in the mouse hypothalamus induced by acute administration of ethanol. J Neurochem 45:1880–1885
50. Prell GD, Bielkiewicz B, Mazurkiewicz-Kwilecki IM (1982) Rat brain histamine concentration, synthesis and metabolism: effect of acute ethanol administration. Prog Neuro-psychopharmacol Biol Psychiatry 6:427–432
51. Smith A, Watson CJ, Frantz KJ, Eppler B, Kennedy RT, Peris J (2004) Differential increase in taurine levels by low-dose ethanol in the dorsal and ventral striatum revealed by microdialysis with on-line capillary electrophoresis. Alcohol Clin Exp Res 28:1028–1038
52. Roberto M, Madamba SG, Stouffer DG, Parsons LH, Siggins GR (2004) Increased GABA release in the central amygdala of ethanol-dependent rats. J Neurosci 24:10159–10166