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The sedative effects of hops *(Humulus lupulus)*, a component of beer, on the activity/rest rhythm

L Franco[1], C Sánchez[1], R Bravo[1], A Rodriguez[1], C Barriga[1], JC Cubero[1,2]

[1]Research Group: Neuroimmunophysiology & Chrononutrition Department of Physiology, Science Faculty,
[2]Health Education Lab., Experimental Science Education Area, University of Extremadura, Badajoz, Spain

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The hop *(Humulus lupulus)*, a component of beer, is a sedative plant whose pharmacological activity is due principally to its bitter resins, especially to the α-acid component 2-methyl-3-buten-2-ol. The mechanism of action of the resin of hop consists of increasing the activity of the neurotransmitter γ-aminobutyric (GABA), inhibiting the central nervous system (CNS). *Objectives:* To analyze in an experimental model of diurnal animal the sedative effect of hop, a component of beer, on the activity/rest rhythm. *Methods:* Experiments were performed with common quail *(Coturnix coturnix)* similar to humans in the sleep-wake rhythm, isolated in 25 × 25 × 25 cm methacrylate cages, with food and water *ad libitum*, in a room with artificial ventilation (22 ± 1 °C) and a lighting cycle of 12L/12D ($n = 5$). The doses administered, close to the content of non-alcoholic beer, were 1, 2 and 11 mg extract of hop as one capsule per day, at 18:00 h for one week. A control group received capsules only with a methylcellulose excipient and a basal group received no treatment. The chronobiological analysis of the animals' activity captured and logged by the software DAS24 was performed using the Ritme computer program (cosinor methods). *Results:* With the dose of 2 mg, there was a statistically significant ($p < 0.05$) reduction of the arithmetic mean nocturnal activity (23 ± 3.0) with respect to the basal (38.56 ± 2.79), control (38.1 ± 2.8) and other doses groups 1 mg (52.04 ± 3.65) and 11 mg (47.47 ± 5.88). This dose of 2 mg, similar to the concentration in beer, was more effective in reducing nocturnal activity than the other doses of 1 and 11 mg, as well as preserving the circadian activity/rest rhythm. *Conclusion:* The concentration of 2 mg of hop extract effectively decreased nocturnal activity in the circadian activity rhythm. On the basis of this investigation, administration of non-alcoholic beer would be recommended due to its hop content and consequent sedative action, which would be an aid to nocturnal sleep.

Keywords: hops, nutrition, beer, sleep

Hops, beer and sleep

The hop *(Humulus lupulus)* is a plant used in the brewery industry for its aromatic characteristics. It has also traditionally been used for its soothing properties. Its sedative activity lies mainly in its bitter resins and in particular in the products of oxidative degradation, such as those resulting from the degradation of α-acids, a major example being 2-methyl-3-buten-2-ol (30). In addition to these bitter degradation products, there are other active components such as xanthohumol (17) and myrcenol (2).The main mechanism of the soothing action of hops is to increase the activity of the neurotransmitter γ-aminobutyric acid (GABA) by modulating brain GABA(A) receptors (17), thus inhibiting the central nervous system (CNS).

Corresponding author: Javier Cubero Juánez, PhD
Experimental Science Education Area, University of Extremadura
Av/de Elvas, sn, CP: 06071, Badajoz, Spain
Phone: +34-924 289300 / ext.: 86576; E-mail: jcubero@unex.es

This sedative effect of hops on the nervous system has been widely reported in animal model studies (4, 13, 30, 31), as also has the narcotic effect of high concentrations of hop extract due to its aforementioned 2-methyl-3-buten-2-ol component (9, 29).

Basic research on hops has been effectively applied to assisting the healthy human population to sleep (8, 28). For example, sedation treatment with valerian and hop combinations (22, 26) has been used to correct temporary sleep onset and sleep interruption disorders. The combination also satisfactorily improved sleep quality in clinical trials with insomnia patients (18) and with patients suffering from non-organic sleep disorder (11). These results reflect the action of components of hops on the inhibitory neurotransmitter GABA(A), an action which can also be exerted by other components of beer (2).

Added to the central effect of hops on GABA, there is an effect on another biomolecule, the hormone melatonin, an endocrine agent that entrains circadian rhythms (15). Neither must one ignore the effect on the neuronal receptors of adenosine which are extensively involved in the mechanism of sleep (1). Therefore, beer and its hop component could enhance the CNS's neuroendocrine response via GABA, adenosine and the indolamine melatonin with an effective sedative action that both entrains the sleep/wake rhythm and favours the induction of sleep.

In sum, beer has numerous components that may have the capacity to both entrain the rhythm of sleep and aid its induction. Given this context, the objective of the present work was to examine the possible sedative action of the levels of hops contained in normal beer and the effect on the activity/rest rhythm, in an animal model physiologically similar to humans in that it is active diurnally.

Methods

Animals

The experimental animals were female young adult quail *(Coturnix coturnix)* of approximately 5 months in age and body weight (b. w.) in the range 246.5–280.5 g (n = 5 per group). These diurnal birds, similar to the human in the sleep-wake rhythm, were housed isolated in cages measuring 25 × 25 × 25 cm and fed *ad libitum*, in a room with artificial ventilation (21 ± 1°C) and lighting (light period from 07:00 to 19:00 h), as described by Sanchez et al. (24). The physiological parameters as the body weight of the animals throughout the trials were measured and also the cloacal temperature by inserting a thermometer to a depth of 3 cm into the cloaca (16).

The study was approved by the Ethical Committee of the University of Extremadura (Badajoz, Spain) in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Hops

Humulus lupulus dry extract (Joh. Barth & Sohn GmbH & Co., Mainburg, Germany) was administered daily for a week at 18:00 h (one hour before the onset of the dark period) in gelatine capsules containing 1, 2 and 11 mg (three different groups). The control group received gelatine capsules containing methylcellulose, daily for a week (Sigma-Aldrich, St. Louis, MO, USA). The basal group did not receive any treatment (their activity pulses were registered for a month). All treatments were performed in duplicate (except the basal group).

Measurement of the activity/rest rhythm

Each cage was equipped with an IR actimeter system to detect activity using two crossed perpendicular infrared beams situated on a plane 70 mm above the sustenance plane. Motor activity counts were automatically logged every 15 min onto a personal computer for each of 7 days of the different experimental groups, and analyzed using the program DAS24© (6, 23).

Chronobiological methods

The chronobiological analysis of the data was performed using the Ritme© for Windows software package. The rhythmicity of each group was studied by cosinor analysis (6). The sinusoidal function used for the fit (1) is the following:

$$y(t) = M + A \times \cos [(2 \times \pi/\tau) \times t - \Phi] \quad (1)$$

where *y(t)* is the value of the cosine function at time *t*, *M* is the mean level of oscillation or the MESOR (acronym of Midline-Estimating Statistic Of Rhythm, the mean value about which the oscillation occurs, equal to the arithmetic mean of equidistant data covering a whole number of cycles), *A* is the amplitude (measure of the extent of a rhythmic change in a cycle as estimated by the sinusoidal function that best fits the data), π is the number pi and τ is the period (24 hours in our case) related to the angular frequency ($\omega = 2 \times \pi/\tau$) and Φ is the acrophase (a phase angle measuring the timing of the peak activity expressed as the lag from a reference time to the crest time of the best fit sinusoidal function). Hence, cosinor analysis determines the best-fitting sinusoidal wave by estimating three parameters: mesor, amplitude and acrophase.

Statistical methods

For the statistical analysis of the data, the software package Graphpad Prism© v. 5.0 was used. Two types of study were carried out:

1. Descriptive, calculating as representative values the arithmetic mean ± standard deviation (SD) and/or confidence limits.

2. Hypothesis testing. Because of the available sample size, a Kolmogorov–Smirnov test was applied to check for the normality of the study variables. The population was found to be normal. The results were analyzed using the Tukey test for multiple comparisons of balanced groups, with the significance level taken to be $p < 0.05$.

Results

During the trials, the animals presented no sign of alteration in their physiological parameters. Their mean body weight and cloacal temperature of trials were 263.5 ± 17 g and 41.4 ± 0.92°C and none of the physiological parameters throughout the week did show significant statistical changes.

Measurements were made of the diurnal (07:00 to 19:00 h) and nocturnal (19:00 to 07:00 h) locomotor activity of the experimental groups administered the different concentrations of hop extract, the basal untreated group and the control group.

Figure 1 shows the nocturnal (19:00 to 07:00 h) motor activity during a week. It was significantly ($p < 0.05$) reduced with the administration of 2 mg of hop extract (23 ± 3) compared to the basal (38.56 ± 2.79), control (38.14 ± 2.78), 1 mg (54.04 ± 3.65) and 11 mg (47.47 ± 5.88) groups. Also, the 1 mg group showed a significant ($p < 0.05$) increase in activity relative to the basal group.

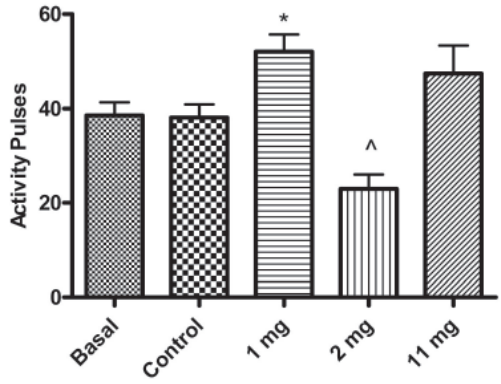

Fig. 1. The nocturnal (19:00–07:00 h) activity pulses (mean ± SE) recorded in each treatment group (1 mg, 2 mg, 11 mg, respectively, to 3.80, 7.60, 41.8 mg/kg b. w.) during a week. * $p < 0.05$ with respect to the basal value; ^ $p < 0.05$ with respect to the other groups ($n = 5$)

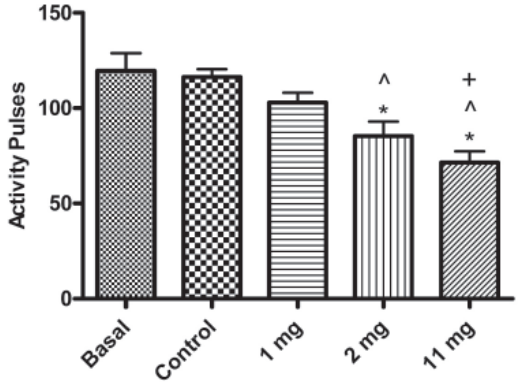

Fig. 2. The diurnal (07:00–19:00 h) activity pulses (mean ± SE) recorded in each treatment group (1 mg, 2 mg, 11 mg, respectively, to 3.80, 7.60, 41.8 mg/kg b. w.) during a week. * $p < 0.05$ with respect to the basal value; ^ $p < 0.05$ with respect to the control value; + $p < 0.05$ with respect to the 1 mg treatment ($n = 5$)

Figure 2 shows the results for the diurnal (07:00 to 19:00 h) motor activity during a week. The 2-mg dose group showed a significant ($p < 0.05$) decrease in motor activity (85.21 ± 7.71) compared to the basal (119.6 ± 9.22) and control (116.3 ± 4.15) groups. The 11 mg group also showed a significant ($p < 0.05$) reduction (71.46 ± 5.81) compared to the basal (119.6 ± 9.22), control (116.3 ± 4.15) and 1 mg (103 ± 5.12) groups.

Table I presents the results of the cosinor analysis of the chronobiological parameters for the different groups. There stands out the decline in the MESOR parameter after the 7 days administration of the 2 mg per day dose (50.60 [45.21–56.04] activity pulses) compared with the other groups. The acrophase with this 2-mg dose remained unchanged (12:08 h [11:11 to 13:05 h]), being very similar to those of the other groups. Hence, as was the case with the nocturnal activity considered alone, the greatest decrease occurs with a dose rate of 2-mg hop extract per day, a dose that is similar to the hop content of beer.

Table I. Chronobiological parameters of each treatment group over a 24-hour period

Treatment	MESOR	Amplitude	Acrophase	*p*-value
Basal	76.14 (66.74–85.54)	69.49 (52.30–86.69)	11:09 (10:13–12:03)	0.000*
Control	78.96 (43.30–88.65)	60.65 (43.30–78.00)	12:02 (10:55–13:08)	0.000*
1 mg	75.83 (65.13–86.53)	41.54 (22.38–60.70)	12:13 (10:23–14:03)	0.000*
2 mg	50.62 (45.21–56.04)	39.54 (29.84–49.24)	12:08 (11:11–13:05)	0.000*
11 mg	58.88 (52.53–65.22)	17.03 (5.67–28.38)	12:41 (9.53–15:28)	0.003*

MESOR values and amplitudes are in the corresponding parameter units (activity pulses). Acrophases are given as times of day (07:00 h–19:00 h–07:00 h light-dark cycle). Confidence limits are in parentheses. The *p*-value indicates significance of the fit of the cosine curve to the data. * $p \leq 0.05$ was considered statistically significant ($n = 5$)

Discussion

The effect of hops on sleep has been amply confirmed in both experimental animal models and human clinical trials. A recent review is given by Zanoli (30). However, the levels of this Cannabaceae in beer would be sufficient to exert a sedative action in the organism?

In normal beer, the concentration of hops is about 0.3% (10). Therefore a moderate intake of beer of two 1/3-litre portions per day (666 ml), an amount recommended by several medical scientific societies (20, 24), would contribute about 2 g of hop extract equivalent per day, or 25.7 mg/kg in an average body weight human.

In the 1970s, Bravo et al. (3) showed that there was a significant decrease in motor activity in mice after the intraperitoneal administration of hop extract, although at high doses. Subsequently, its analgesic effect and the decrease in spontaneous motor activity were confirmed also in a mouse model, with there being an enhancement in the induction of sleep by pentobarbital (13).

Given that the average body weight of our experimental animals was 263.5 ± 17 g, the administration doses used in the experiment (1, 2 and 11 mg hop extract per capsule per day) were equivalent to 3.80, 7.60 and 41.80 mg/kg b. w. Our study showed an evident decline in motor activity over a 24-h period, reflected in the decreased values of the MESOR parameter with the 2 mg and 11 mg doses (which correspond to 7.60 mg/kg b. w. and 41.8 mg/kg b. w., respectively).

There is the drawback with the highest dose, however, that the decline in activity does not occur in the desired period, i.e., at night, but is delayed until the following diurnal period. Possibly, the bitter β-acid fraction of the hops is exerting its wakefulness action (31), an effect that appears to be controlled in our treatment with a 2 mg (7.60 mg/kg) dose since this produces the decline in activity after administration, i.e. at night, sedation that is maintained until the diurnal period, although to a lesser degree.

The present results in quail a diurnal animal model similar to the human in the sleep-wake rhythm, with the 2 mg dose having a sedative effect in both the nocturnal and diurnal periods, are consistent with the study reported by Zanoli et al. (32) in which the oral administration of hop extracts to mice achieved a reduction in spontaneous locomotor activity. In particular, those workers used an extract concentration of 10 mg/kg b. w., equivalent to 2 mg per animal. They observed its central sedative effect in the increased sleep time and reduced motility compared to their control animals. Thus, essentially the same doses were used in that experiment and in ours, giving results that are consistent with each other (4).

A substantially higher concentration of hop extract (800 mg/kg b. w. = 160 mg dose) administered in association with anæsthetics and hypnotics, such as ketamine, led to prolonged states of deep narcosis (27). Similarly, the product of the oxidative degradation of the α-acid content of fresh hops, 2-methyl-3-buten-2-ol, applied to mice at concentrations of 0.8 g/kg b. w. produced narcosis that lasted 8 hours (9).

The biphasic animal model used in the present study, the common quail, has, like humans, a nocturnal period of sleep and diurnal activity. The results thus suggest that, because of its hop content, beer may have a possible use as a sedative in humans. The mechanism would principally be by modulating the GABAergic response, in addition to the effects of the hop components myrcenol (2), xanthohumol and such α-acid derivates (30) as 2-methyl-3-buten-2-ol.

The sedative property of hops has been confirmed in humans when acting in combination with valerian (*Valeriana officinalis*), with the two acting synergically on the sedative function (5, 8, 21, 22, 28). Schellenberg et al. (25) studied the combined effect of hops and valerian on the central adenosine mechanism, observing an increase in alpha waves on the EEG, with sleep inducers being generated through the adenosine receptors. To this action on adenosine (1), one must also add the effect on the CNS the hormone melatonin (12, 15), which are involved in sleep and circadian rhythms, respectively.

Through its hop content, alcohol-free beer could exert a sedative action in humans, apart from its benefits for health when consumed in moderation (14), among which are its anti-cancerogenous (7) and cardiovascular health (19) properties. One can therefore conclude that a moderate consumption of beer will favour night-time rest, due in particular to its hop components, in addition to its other confirmed benefits for the organism.

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