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ORIGINAL ARTICLE

Effect of day/night administration of three different inhalational anesthetics on melatonin levels in rats

Elvan Ocmen [a,*], Hale Aksu Erdost [a], Leyla S. Duru [a], Pinar Akan [b], Dilek Cimrin [b], Ali N. Gokmen [a]

[a] Department of Anesthesiology, Dokuz Eylul University, Izmir, Turkey
[b] Department of Biochemistry, Dokuz Eylul University, Izmir, Turkey

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Abstract The nocturnal peak of melatonin can be altered after anesthesia and surgery. We aimed to examine the melatonin levels during the day and night after anesthesia with three commonly used inhalational anesthetics. Forty-eight male Wistar albino rats were randomized into eight groups. Rats were administered anesthesia between 7:00 AM and 1:00 PM (day groups) or 7:00 PM and 1:00 AM (night groups) for 6 hours. At the end of the anesthesia, blood samples were collected for assessing melatonin levels. Mean values of melatonin levels after 6 hours of anesthesia during daytime were 43.17 ± 12.95 for control, 59.79 ± 27.83 for isoflurane, 50.75 ± 34.28 for sevoflurane and 212.20 ± 49.56 pg/mL for desflurane groups. The night groups' mean melatonin levels were 136.12 ± 33.20 for control, 139.85 ± 56.29 for isoflurane, 117.48 ± 82.39 for sevoflurane and 128.70 ± 44.63 pg/mL for desflurane groups. Desflurane anesthesia between 7:00 AM and 1:00 PM significantly increased melatonin levels ($p < 0.001$). Sevoflurane and desflurane anesthesia between 7:00 PM and 1:00 AM decreased the melatonin levels but there were no significant differences ($p = 0.904$ and $p > 0.99$, respectively). Isoflurane anesthesia did not significantly change melatonin levels during day or night ($p = 0.718$ and $p > 0.99$, respectively). Our results demonstrate that during daytime desflurane anesthesia can alter melatonin levels. Altered melatonin rhythm following inhalational anesthesia can be related to sleep disorders observed after anesthesia.

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Anesthesiology, Dokuz Eylül University School of Medicine, 35340 Inciralti, Izmir, Turkey.
E-mail address: elvan.sahin@gmail.com (E. Ocmen).

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Introduction

Melatonin is a hormone that has a nocturnal peak. Melatonin secretion is controlled by suprachiasmatic nuclei (SCN), which has a circadian clock regulated by day/night cycles. Reduced or asynchronous melatonin levels can be associated with aging of the organism and depression [1,2]. It is also known that melatonin regulates the sleep/wake cycles [2,3] so the influences of this hormone's rhythm can be responsible for sleep disturbances, drowsiness, fatigue and delirium after anesthesia and surgery [4].

General anesthesia is a sleep—awake condition which is thought to alter circadian rhythms. It has been shown that anesthesia with or without surgery can influence the circadian rhythm of melatonin [1,5—7]. We previously found that in 15-day-old rats the administration of isoflurane during the day increases melatonin levels while administration at night has no effect [8]. Likewise, sevoflurane anesthesia during day and night hours increases melatonin levels in 15-day-old rats (unpublished observations).

We hypothesized that day administration of inhalational anesthetics could alter the circadian rhythm of melatonin but night administration could conserve this rhythm. The aim of this experimental study was to investigate the effects of the three commonly used inhalational anesthetics: sevoflurane, isoflurane and desflurane, on melatonin levels administered over day/night cycles.

Methods

After the approval of the ethics committee of Dokuz Eylul University (approval no: 09/2013), 48 male Wistar albino rats weighted between 200—250 g were included in this experimental study. Until the experiment, the subjects were kept under standard laboratory conditions (12 hours light—12 hours dark, 20—22°C and 50—60% humidity). All efforts to reduce the number of animals and their suffering were made.

Rats were randomized into control and anesthesia groups. Desflurane (Desfluran, Abbott Laboratories, Istanbul, Turkey), sevoflurane (Sevofluran, Vapor 19.1, Abbott Laboratories, Wiesbaden, Germany) and isoflurane (Forane, Abbott Laboratories, Istanbul, Turkey) were used for anesthesia. Night groups inhaled 6 L/min oxygen (control) or 1 minimum alveolar concentration (MAC) of inhalational anesthetics (5.7% desflurane, 1.97% sevoflurane and 1.1% isoflurane [9,10]) between 7:00 PM and 1:00 AM. In the day groups, experiments were performed between 7:00 AM and 1:00 PM. The research was conducted in the spring. There were six rats in each group.

During the night hours the lights were not on and all of the procedures were done in the dark with red light. It has been shown that red light does not alter the circadian rhythm of rats [7].

Anesthesia apparatus, induction and maintenance

Separate glass jars for every single rat were used as anesthesia apparatus. The jar volume was 450 mL. All jars had gas-in and gas-out systems. Every inhalational anesthetic was administered by its own vaporizator. Inspired oxygen and volatile agent concentrations were monitored (Anesthesia Gas Monitoring 1304, Brüel & Kjær Sound & Vibration Measurement A/S, Nærum, Denmark) and kept constant, and respiratory effort and skin color were also inspected during the study period. All jars were placed in a water-bath with a constant temperature of 37°C.

At the end of the anesthesia blood samples were taken and rats were euthanized by decapitation. Control animals were administered isoflurane for a short time before blood samples were taken and euthanized.

Melatonin measurement

In the laboratory, blood samples were centrifuged at + 4°C (3000 g) (Hettich Zentrifugen Mikro 22 R, Tuttlingen, Germany) for 10 minutes. Plasma samples were pipetted into Eppendorff tubes and kept at −80°C until assay. Melatonin was tested with a rat melatonin radioimmunoassay (RIA) kit (Melatonin Research, RIA, Labor Diagnostica Nord GmbH, Nordhorn, Germany) using the RIA method at the laboratory of Department of Biochemistry, Faculty of Medicine, Dokuz Eylul University.

Statistical analysis

Statistical analysis was performed using SPSS for Windows statistical program, version 15.0 (SPSS Inc., Chicago, IL, USA). Results were given as mean ± SD. In the statistical analysis of melatonin values, Levene's test was used for homogeneity of group variances, and the distribution was considered homogeneous with values of $p > 0.05$. One-way ANOVA posthoc Dunnett tests were used for comparisons between the groups. The Student t test was used to compare day and night groups. A value of $p < 0.05$ was considered statistically significant.

Results

Forty-eight rats were included into the study and none of the animals died during the study protocol.

Melatonin levels did not alter compared to the control group following sevoflurane and isoflurane anesthesia during the day hours ($p = 0.959$ and $p = 0.718$, respectively). The control group's mean melatonin level was 43.17 ± 12.95 pg/mL. Mean melatonin levels were 50.75 ± 34.28 pg/mL after sevoflurane and 59.79 ± 27.83 pg/mL after isoflurane anesthesia. However, after desflurane anesthesia between 7:00 AM and 1:00 PM, the mean melatonin level (212.20 ± 49.55 pg/mL) was increased significantly compared to the control group ($p < 0.001$) (Figure 1).

During the night hours sevoflurane, isoflurane or desflurane anesthesia did not change the melatonin levels significantly ($p = 0.904$, $p > 0.99$ and $p > 0.99$, respectively). Mean melatonin values were 136.12 ± 33.20 pg/mL, 139.84 ± 56.29 pg/mL, 117.47 ± 82.39 pg/mL and 128.70 ± 44.63 pg/mL for control, isoflurane, sevoflurane and desflurane groups, respectively.

Night control, isoflurane and desflurane groups' melatonin levels were significantly higher compared with their daytime groups ($p < 0.001$, $p = 0.013$ and $p = 0.016$, respectively). We could not find a statistically significant