Journal of Pharmacological Sciences 131 (2016) 68–71

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Short communication

Sevoflurane-induced pica in female rats

Kouichi Yamamoto [a, *], Emiri Yamamoto [b], Toru Sugimoto [a], Takuya Sagakami [a], Atsushi Yamatodani [c]

[a] Department of Medical Science and Technology, Division of Health Sciences, Graduate School of Medicine, Osaka University, 1-7 Yamadaoka, Suita, Osaka 565-0871, Japan
[b] Department of Anesthesiology, Kaizuka City Hospital, 3-10-20 Hori, Kaizuka, Osaka 597-0015, Japan
[c] Osaka University, 1-7 Yamadaoka, Suita, Osaka 565-0871, Japan

ARTICLE INFO

Article history:
Received 27 January 2016
Received in revised form
2 March 2016
Accepted 17 March 2016
Available online 12 April 2016

Keywords:
Anti-emetic drugs
Pica
Postoperative nausea and vomiting

ABSTRACT

We examined the effects of volatile anesthetics on pica, which can be used to assess nausea and vomiting in rats. We found that inhalation anesthesia with sevoflurane significantly induced pica in female but not male rats. Among the female rats, young rats (8 weeks old) were more susceptible to its induction than adult rats (20 weeks old) with ovariectomy or sham-surgery. Anti-emetic drugs that are used to prevent postoperative nausea and vomiting (PONV) inhibited the pica. These results suggest that sevoflurane-induced pica in young female rats has the potential to be an animal model of PONV in humans.

Postoperative nausea and vomiting (PONV) occur in 30% of patients receiving surgery under general anesthesia (1). Risk factors of PONV are considered to be a female sex, younger age, past history of PONV and/or motion sickness, non-smoking status, the duration and type of anesthetics, and postoperative use of opioids (2). Serotonin 5-HT_3, dopamine D_2, histamine H_1, neurokinin NK_1 receptor antagonists, and corticosteroids are used to reduce the incidence (3); however, patients often experience PONV despite the administration of these anti-emetic drugs (4). To elucidate its etiology, the objective evaluation of this symptom in experimental animals is required. Rats are assumed to be unsuitable for the purpose because they do not vomit. However, we have proposed that emetic stimulus-induced pica, a craving to eat non-food materials such as kaolin, in rats can be used as an assessment of nausea and vomiting in humans (5, 6). We investigated the effects of sevoflurane on the development of pica and examined the effects of anti-emetic drugs on this anesthetic-induced pica.

All experimental protocols were approved in accordance with the Animal Experimental Committee of Osaka University. Naive male (6 weeks old, body weight: 190–220 g) and female (8 weeks old, body weight: 180–210 g) Wistar/ST rats were obtained from Japan SLC (Shizuoka) and housed in individual home cages (25 × 20 × 20 cm) in a room with a regular light/dark cycle (lights on 6:00–18:00) at a constant temperature (approximately 24 °C) and humidity (approximately 50%). During habituation and the experimental period, rats were allowed free access to water, commercially available standard chow (CE-2, CLEA Japan, Inc., Tokyo), and handmade kaolin pellets prepared according to a previously reported method (6). The food pellets and kaolin were provided in their respective stainless steel containers (5 × 5 × 10 cm) placed in the home cage. After more than one week of habituation, the rats were administered sevoflurane (Pfizer Japan Inc., Tokyo). The anesthetic method was as follows. Rats were placed in a sealed acrylic box (40 × 40 × 30 cm) and exposed to 3% sevoflurane using a vaporizer (BS-400T; Brain Science Idea Co., Ltd., Osaka) for induction. After the confirmation of immobilization, rats were removed from the acrylic box and continuously exposed to 1.5% sevoflurane with a rodent face mask. The concentration of sevoflurane was determined by confirmation of the loss of the righting reflex in each rat. To maintain a core temperature of around 37 °C, all rats were placed on a heating pad during anesthesia, and the body temperature was monitored using a rectal probe. The duration of sevoflurane anesthesia was varied at 1, 3, and 6 h. The time when the sevoflurane anesthesia was stopped was set in accordance with the start time of the dark phase (at

* Corresponding author. Tel./fax: +81 6 6879 2577.
E-mail address: kouichi@sahs.med.osaka-u.ac.jp (K. Yamamoto).
Peer review under responsibility of Japanese Pharmacological Society.

http://dx.doi.org/10.1016/j.jphs.2016.03.015

18:00). All rats were immediately returned to their home cage. For the control study, rats were placed in the box without anesthesia for 6 h. Daily food and kaolin intakes and the body weight were measured on the day before and after receiving the anesthetic agents. Spilt food and kaolin were collected and weighed to accurately calculate consumption. Food and kaolin weights were measured to the nearest 0.01 g. There were six rats in each of the experimental groups. In this study, the estrus cycles of female rats were not considered throughout the experiment.

In another series of experiments, bilateral ovariectomized rats (OVX-rats, body weight: 300–330 g) or sham-surgery rats (sham-operated, body weight: 250–280 g) were administered sevoflurane anesthesia for 6 h. Ovariectomized rats were used as a model of the menopausal state. Their daily food and kaolin intakes and body weight were measured on the day before and after receiving the anesthetic agents. The general experimental protocol was the same as described above. The surgical procedure was according to a previously reported method (6). There were four rats in each of the experimental groups. Female rats (8 weeks old) were intraperitoneally injected with granisetron (0.1 and 0.5 mg/kg), prochlorperazine (1 and 5 mg/kg), fosaprepitant (1 and 2 mg/kg), diphenhydramine (10 and 20 mg/kg), or dexamethasone (0.5 and 1 mg/kg) simultaneously at the end of sevoflurane anesthesia, and their kaolin and food consumption levels were measured after 24 h. All commercialized anti-emetic drugs purchased from pharmaceutical companies were dissolved in physiological saline. The doses of anti-emetic drugs are expressed as the free base and were selected according to the published data (6, 7). Control animals intraperitoneally received saline (1 mL/kg body weight). There were five rats in each of the experimental groups. Data are expressed as mean values ± S.D. Two-way factorial analysis of variance (ANOVA) followed by Bonferroni's post-hoc test was used for the comparison between male and female rats. Differences in the results from experiments on OVX rats and anti-emetic drugs were analyzed using the non-parametric Mann–Whitney U test and one-way ANOVA, followed by post-hoc Dunnett's multiple comparison test, as appropriate. A P-value of less than 0.05 was considered significant.

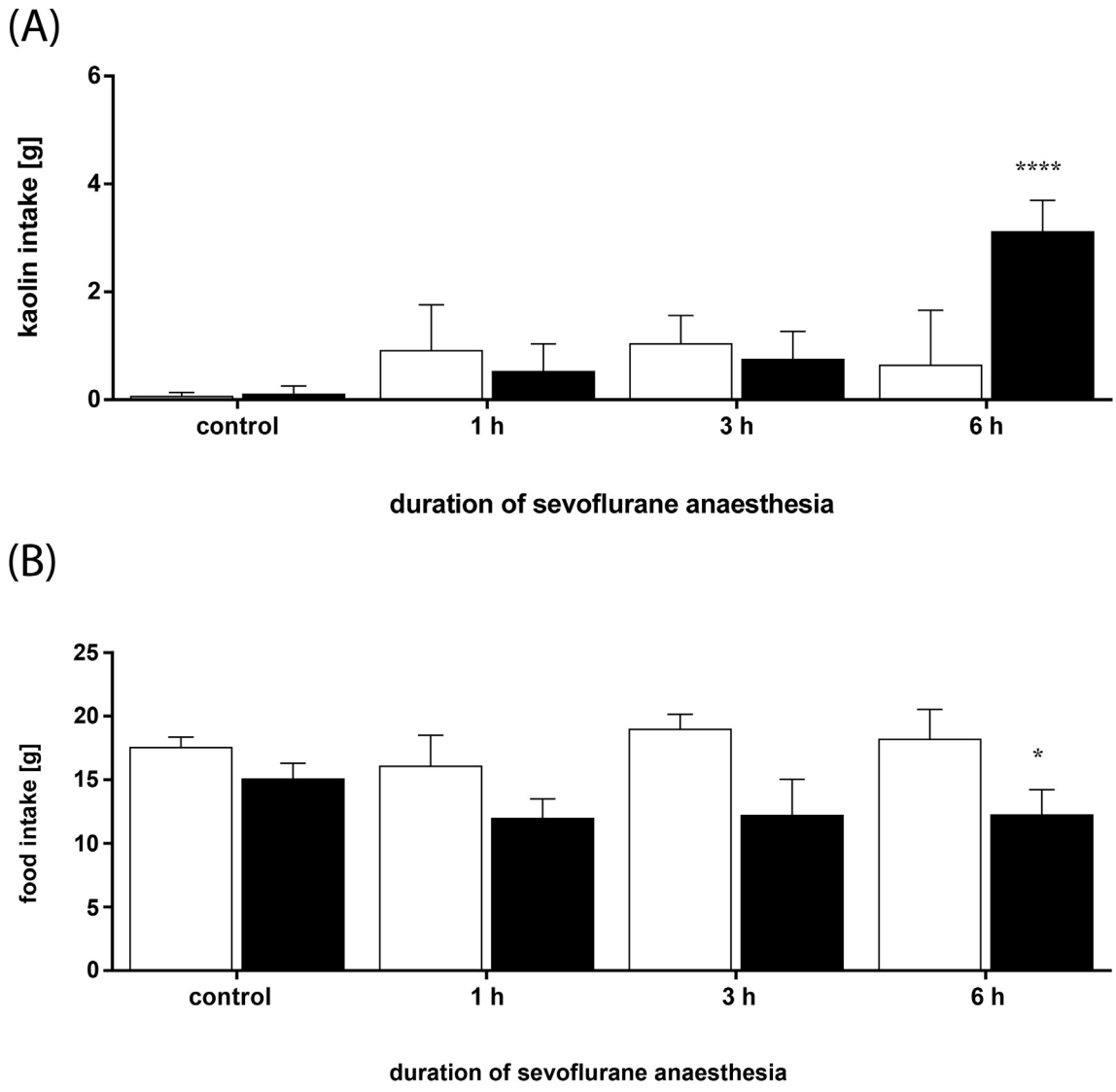

Fig. 1. The effect of sevoflurane on (A) kaolin and (B) food intakes in male and female rats. There were six rats in each of the experimental groups. Sevoflurane (1.5%) was administered using inhalation equipment. The duration of anesthesia was varied at 1, 3, and 6 h. Columns and bars represent the mean ± SD of each cumulative intake measured 24 h after sevoflurane administration. The data were analyzed for significant differences using two-way analysis of variance (ANOVA), followed by *post-hoc* Bonferroni's multiple comparison tests. $^{*}P < 0.05$ and $^{****}P < 0.0001$ vs. control group.