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Rebound insomnia induced by abrupt withdrawal of hypnotics in sleep-disturbed rats

Masahiro Hirase, Takayuki Ishida, Chiaki Kamei *

Department of Medicinal Pharmacology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8530, Japan

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ABSTRACT

The present study was performed to examine whether or not rebound insomnia is caused by an abrupt withdrawal of benzodiazepine hypnotics and tandospirone in rats. Etizolam and triazolam caused a significant shortening of sleep latency, increase in non-REM sleep time, and decrease in wake time in a dose-dependent manner. Etizolam and triazolam caused a significant shortening of sleep latency during drug administration (for 7 days), whereas a significant prolongation of sleep latency was observed by the abrupt withdrawal of these drugs. Tandospirone caused a shortening of sleep latency, whereas no effect was observed on non-REM sleep time and wake time during drug administration (for 7 days). On the other hand, tandospirone showed no significant effect on sleep latency through its abrupt withdrawal, differing from etizolam and triazolam. From these findings, a rebound phenomenon in terms of sleep latency was confirmed with etizolam and triazolam in rats. Furthermore, the 5-HT_{1A} agonist, tandospirone, caused no rebound phenomenon regarding sleep latency in rats.

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1. Introduction

About 30–50% of the population complains of sleep-related problems (Quera-Salva et al., 1991; Weyere and Dilling, 1991). Insomnia is a well-known disorder categorized by a difficulty in falling asleep, intermittent waking after falling asleep, and early morning awakening. A number of benzodiazepines and benzodiazepine analogues are used to treat insomnia as hypnotic drugs. These drugs are useful due to both their safety and effectiveness. On the other hand, it has been reported that the discontinuation of hypnotics causes withdrawal symptoms such as rebound insomnia (Cimolai, 2007; Voshaar et al., 2004; Bixler et al., 1977; Fyer et al., 1987). Furthermore, it has been reported that a gradual tapering of the benzodiazepine dosage did not fully resolve withdrawal symptoms (Rikels et al., 1990; Schweizer et al., 1990). Based on these findings, there is regarding increasing interest in the use of alternative medicines. There have been many reports about the withdrawal symptoms after the chronic administration of benzodiazepines. However, most of these studies involved humans, and there have been few studies on the sleep–wake cycle following the abrupt withdrawal of benzodiazepines using animals. In a previous study, we reported that a sleep-disturbed model was useful for evaluating the effects of benzodiazepines on the sleep–wake cycle by placing rats on a grid suspended over water (Shinomiya et al., 2003). In addition, this model was also useful for testing the effect of tandospirone, a 5-HT_{1A} agonist, on the sleep–wake cycle (Utsu et al., 2007). Therefore, we chose two antianxiety drugs: etizolam ($t_{1/2}$=6.9 h) and tandospirone ($t_{1/2}$=1.2 h). In addition, we confirmed whether our method is useful for evaluating rebound insomnia caused by abrupt withdrawal using triazolam ($t_{1/2}$=4.3 h), which has been reported recognized to cause rebound insomnia in rats (Voderholzer et al., 2001).

The present study was designed to confirm whether benzodiazepines and tandospirone cause rebound insomnia by abrupt withdrawal in rats.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 220–300 g (Japan SLC, Shizuoka, Japan) were used. All animals were maintained in an air-conditioned room with a controlled temperature (24±2 °C) and humidity (55±15%). They were housed in an aluminum cage with sawdust and kept under a light/dark cycle (lights on from 7:00 to 19:00). The animals were allowed free access to food and water except during the experiments. All procedures involving the animals were conducted in accordance with the Guidelines for Animal Experiments at Okayama University Advanced Science Research Centers, and all procedures were licensed by the Animal Research Control Committee of Okayama University.

2.2. Surgery

The animals were anesthetized with pentobarbital sodium (Nembutal®, 35 mg/kg, i.p., Abbott Laboratories, North Chicago, IL, USA), then fixed to a stereotaxic apparatus (SR-5, Narishige, Tokyo, Japan). For electroencephalogram (EEG) recording, a stainless steel screw electrode was chronically implanted into the right frontal cortex (A: 0.5, L: 3.0) according to the atlas of Paxinos and Watson (2007). A

* Corresponding author. Tel./fax: +81 86 2517939.
E-mail address: kamei@pheasant.pharm.okayama-u.ac.jp (C. Kamei).

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stainless steel screw fixed in the left frontal bone served as a reference electrode. To record the electromyogram (EMG), stainless steel wire electrodes (0.2 mm in diameter) were implanted into the dorsal neck muscle. The electrodes were connected to a miniature receptacle and the whole assembly was fixed to the skull with dental cement. At least 7 days were allowed for recovery from the surgery.

2.3. EEG and EMG recording

EEG and EMG were recorded with an electroencephalogram (Model EEG 5113, Nihon Koden, Tokyo, Japan) from 9:30 to 15:30. The recording was carried out according to the method described previously (Huang et al., 2001; Tokunaga et al., 2007). The signals were amplified and filtered (EEG, 0.5–30 Hz; EMG, 16–128 Hz), then digitized at a sampling rate of 128 Hz and recorded using the data acquisition program SleepSign ver. 2.0 (Kissei Comtec, Nagano, Japan). EEG and EMG of rats were measured in an observation cage (diameter, 26 cm; height, 31 cm), with its floor placed on a stainless steel grid. The grid floor was placed inside the plastic cage. The stainless steel rods of the grid (3 mm wide) were set 2 cm apart. The cage was filled with water up to 1 cm below the grid surface. The observation cage was placed in a sound-proof and electrically shielded box (70×60×60 cm). The rats were housed in a home cage (with sawdust) and then rats were placed on an observation cage with a stainless steel grid at the time of the experiment.

2.4. Sleep–wake state analysis

Sleep–wake states were automatically classified by 10-s epochs as awake, non-rapid eye movement (non-REM), or REM sleep by SleepSign ver. 2.0, according to the criteria previously described (Shinomiya et al., 2003; Shigemoto et al., 2004). As a final step, defined sleep–wake stages were examined visually and corrected if necessary. Each state was characterized as follows: wake, low-amplitude EEG and high-voltage EMG activities; non-REM sleep, high-amplitude slow or spindle EEG and low-voltage EMG activities; REM sleep, low-voltage EEG and EMG activities.

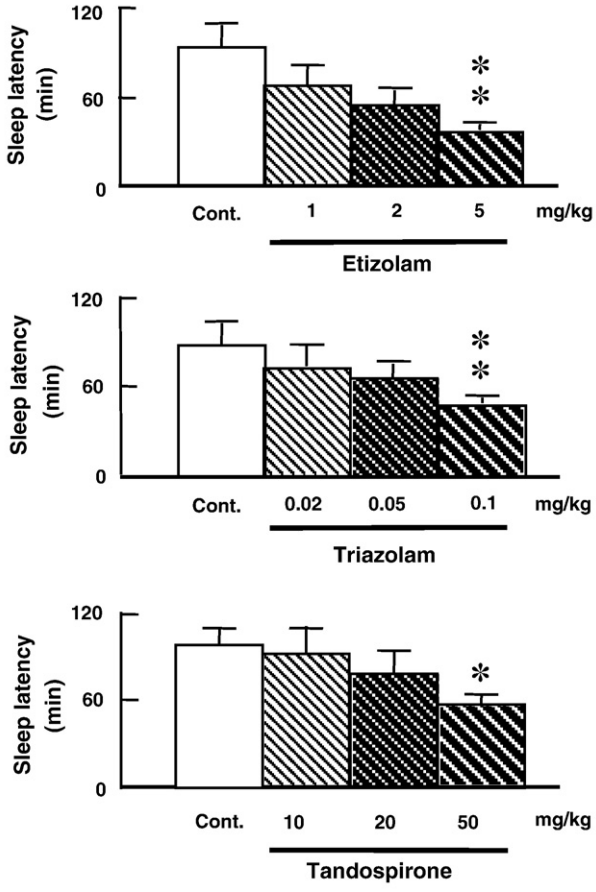

Fig. 1. Effects of etizolam, triazolam, and tandospirone on sleep latency. Columns and vertical bars represent the means±S.E.M. (n=8). Drugs were administered orally. *, **: Significantly different from control group at P<0.05 and P<0.01, respectively.

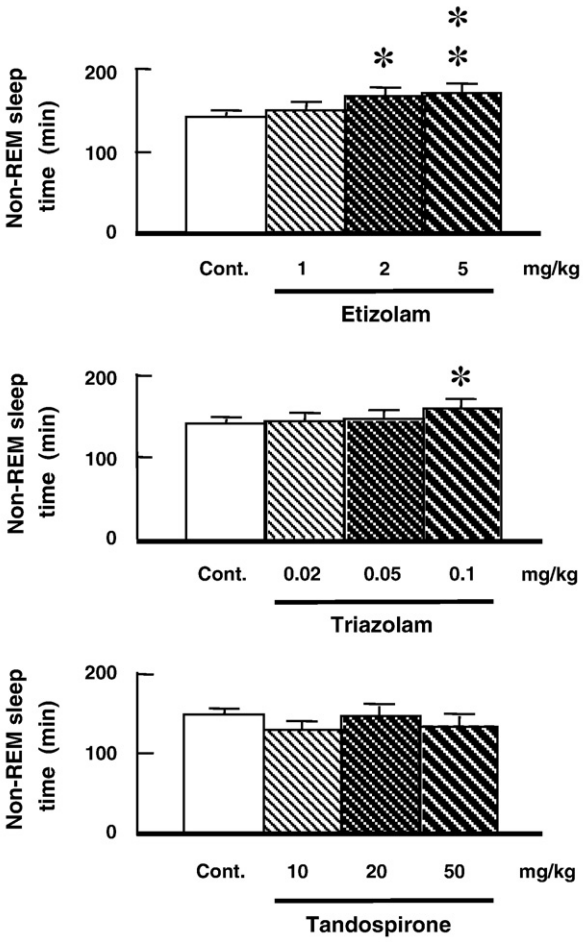

Fig. 2. Effects of etizolam, triazolam, and tandospirone on non-REM sleep time. Columns and vertical bars represent means±S.E.M. (n=8). Drugs were administered orally. *, **: Significantly different from control group at P<0.05 and P<0.01, respectively.

2.5. Drugs

The following drugs were used: etizolam (Depas®, Mitsubishi Tanabe, Osaka, Japan), triazolam (Halcion®, Pfizer, NY, USA), and tandospirone (Sediel®, Dainippon Sumitomo, Osaka, Japan). Etizolam, triazolam, and tandospirone were suspended in 0.5% carboxymethyl cellulose sodium solution. The drugs were administered orally at 9:30. EEG and EMG were measured for 6 h after drug administration.

2.6. Method for chronic administration

The experimental protocol took place over 12 consecutive days. Etizolam, triazolam, and tandospirone were administered at 9:30 daily for 7 days. EEG and EMG were recorded once a day with an electroencephalogram (Model EEG 5113, Nihon Koden, Tokyo, Japan) from 9:30 to 15:30 for 12 consecutive days.

2.7. Data analysis and statistics

Values shown are means±S.E.M. One-way analysis of variance (ANOVA) with Dunnett's test was used for a estimating the drug effects.

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