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Research report

Effects of eszopiclone and zolpidem on sleep–wake behavior, anxiety-like behavior and contextual memory in rats

Max P. Huang[a], Kushan Radadia[a], Brian W. Macone[a], Sanford H. Auerbach[a,b], Subimal Datta[a,b,c,*]

[a] Laboratory of Sleep and Cognitive Neurosciences, Department of Psychiatry, Boston University School of Medicine, 85 East Newton Street, M-902, Boston, MA 02118, USA
[b] Department of Neurology, Boston University School of Medicine, 85 East Newton Street, M-902, Boston, MA 02118, USA
[c] Department of Neuroscience, Boston University School of Medicine, 85 East Newton Street, M-902, Boston, MA 02118, USA

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ABSTRACT

At present, eszopiclone and zolpidem are the most commonly prescribed drugs for treating insomnia. Despite the established relationship between sleep disturbance and anxiety, it remains unknown whether targeted treatment for insomnia may affect acute anxiety. Therefore, the objective of this study was to examine the effects of three different doses (1, 3, and 10 mg/kg) of eszopiclone and zolpidem on the states of sleep and wakefulness, levels of anxiety-like behavior, and long-term contextual memory in footshock-induced anxious rats. The results of this study demonstrated that the administration of eszopiclone and zolpidem both were equally effective in attenuating footshock stressor-induced suppression of slow-wave sleep (SWS). The administration of eszopiclone at 1 mg/kg or zolpidem at 1 and 3 mg/kg doses showed a tendency for attenuating stressor-induced suppression of REM sleep. However, the REM sleep attenuating effects of these drugs disappeared when they were administered at higher doses. The administration of eszopiclone at 3 and 10 mg/kg doses and zolpidem at all three doses reduced the power of electroencephalographic theta band frequencies during wakefulness. In addition, the administration of eszopiclone at 1 and 3 mg/kg doses suppressed stressor-induced anxiety-like behavior. The administration of zolpidem at 1, 3, or 10 mg/kg doses was not effective in attenuating stressor-induced anxiety-like behavior. Contextual memory after administration of eszopiclone at 1 mg/kg dose had no effects, but was reduced significantly with increased dosage. Contextual memory after administration of zolpidem, at all three doses, was severely disrupted. The results of this study suggest that eszopiclone at a low dose could be used effectively to control anxiety and anxiety-induced insomnia.

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1. Introduction

Insomnia and generalized anxiety disorder (GAD) are highly prevalent conditions with significant associated distress and morbid consequences [11,50,91,93]. These conditions commonly coexist and have considerable symptomatic overlap. The majority of patients with GAD have at least one form of comorbid sleep disturbance [66,73,94,96]. Additionally, GAD is one of the most common psychiatric comorbidities in individuals with insomnia [61,65]. Most objective clinical studies of sleep disturbances and anxiety have focused primarily on long-term effects of anxiety [50] and have noted an increase in sleep latency, lower percentage of deep sleep and decreased rapid eye movement (REM) density [31,67,85,94]. The immediate effects of anxiety on sleep architecture are considerably more elusive. Insomnia may predispose individuals to develop anxiety disorders [30] or may develop subsequently after the onset of anxiety [44,65,80,81]. Despite an established relationship between insomnia and anxiety, it remains relatively unknown whether targeted treatment of insomnia may affect anxiety.

To study the immediate effects of anxiety, many researchers utilize the rodent model as a convenient method of analyzing behavioral and pharmacological responses to stress. The elevated plus-maze (EPM) is the most extensively used behavioral paradigm to measure anxiety in the rodent model [9,42,53]. Anxiety-related behavior reflects a conflict between the rodent's desire to explore a novel environment and its innate preference to protected areas [106]. The open arm of the EPM is considered anxiogenic, or anxiety-inducing; thus, rats exhibiting greater anxiety-related behavior will enter and spend less time in the open arms of the maze [3,70]. The percentage of time spent on the open arm is increased and decreased with anxiolytic and anxiogenic substances, respectively [3,70,78]. When used appropriately, the EPM is the most effective and popular animal model to observe and quantify anxiety within the rodent model [53,77].

* Corresponding author at: Boston University School of Medicine, 85 East Newton Street, M-902, Boston, MA 02118, USA. Tel.: +1 617 638 5863; fax: +1 617 638 5862.
E-mail address: Subimal@bu.edu (S. Datta).

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The rodent model is also frequently employed to measure the changes in sleep–wake architecture after experimental manipulation of fear-inducing stress [41,43,53,56,99]. Classical fear conditioning, the most common paradigm, utilizes an unconditioned foot-shock presented with a conditioned stimulus to measure the acquisition, expression and/or extinction of fear [43,53,68,99]. Neuroimaging techniques, such as fMRI, have afforded researchers the opportunity to examine the similarities between structures involved in the acquisition and expression of fear in humans and rodents [25]. A number of studies have demonstrated that homologous structures in the human and rat are involved in fear acquisition, an important aspect of anxiety behavior [7,112]. The contextual fear conditioning model is also a popular model to study acquisition, consolidation, and retrieval of memory in rodents [5,16,29]. Numerous other paradigms employ a range of stressors including immobilization, corticosterone administration and open field exposure [98,100,103]. All of these techniques and manipulations have significant effects on sleep–wake behavior, but the degree of behavioral stress is often assumed or unknown.

Benzodiazepines (BZs) have long been used as anxiolytics, and these drugs have also found widespread use in the treatment of a variety of sleep disorders [49,52,62]. BZs work by binding to specific allosteric BZ sites on GABA-A receptors, thereby modulating the function of these receptors [74,75,83,108,109]. Mammalian GABA-A receptors in the central nervous system are pentameric structures consisting of distinct subunits, which can include α1–6, β1–3, and γ1–3 or δ [90]. Classical BZs bind equally well to GABA-A receptors containing all of the α subunit isoforms except α4 and α6 [38,74,108]. In recent years, the use of BZs has been demonstrated to have a number of deleterious side effects such as anterograde amnesia and the potential to build tolerance, dependence, and withdrawal pathologies [27,49,59,62,76]. Awareness of these undesirable effects of BZs resulted in the development of a new generation of nonbenzodiazepine hypnotics, including zolpidem (Zol; Ambien; Sanofi-aventis, Bridgewater, NJ) and eszopiclone (Esz; Lunesta; Sepracor, Marlborough, MA). zolpidem has a high affinity for GABA-A receptors containing the α1 subunit, low affinity for α2- and α3-containing receptors, and no significant affinity for α5-containing receptors [2,38,74,108]. In contrast, eszopiclone exhibits considerable activity at GABA-A receptors containing α1, α2, α3, and α5 subunits [2,13,23,36,38,84,92].

In recent years, a number of studies in both humans [24,28,40,47–49,62,63,82] and animals [10,34,35,54,64,95,110,111] have tested the hypnotic effects of eszopiclone and zolpidem. These studies have suggested that both eszopiclone and zolpidem are nearly equally effective hypnotics with very few or no adverse side effects. One animal study, suggested that eszopiclone might have some anxiolytic action in naïve (not yet subjected to experimental stress) rats [8]. While a number of reports have described the hypnotic effects of eszopiclone and zolpidem in humans and animals, there have been no animal or human studies that have systematically tested and/or compared the effects of eszopiclone and zolpidem on acute anxiety and anxiety-induced changes in the sleep–wake cycle and memory. The changes in the power of delta frequency waves in the cortical EEG is considered to be a physiological indicator of changes in the quality of sleep during slow-wave sleep and intensity of homeostatic sleep pressure during wakefulness [4,43,89]. Similarly, the changes in the power of theta frequency waves in the cortical EEG is considered to be a physiological indicator of changes in the contextual memory processing [16,72]. The present study therefore examines the effects of an intraperitoneal injection of eszopiclone and zolpidem on stressor-induced anxiety-like EPM behavior, changes in the sleep–wake architecture, delta and theta frequency powers in the cortical EEG, and contextual memory in chronically-instrumented freely moving rats.

2. Materials and methods

2.1. Subjects and housing

Experiments were performed on 56 adult male Wistar rats (Charles River Laboratories, Wilmington, MA) weighing between 300 and 375 grams. The rats were housed individually at 24°C with ad libitum access to food and water. Lights were on from 7:00 a.m. to 7:00 p.m. (light cycle) and off from 7:00 p.m. to 7:00 a.m. (dark cycle). The principles for care and use of laboratory animals in research, as outlined by the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (1996), were strictly followed. Additional care was taken to ensure that any potential discomfort and the number of animals used were minimized. To reduce additional stress that might be imposed by the experimental handling, animals were handled daily for 15–20 min between 09:00 a.m. and 10:00 a.m. This habituation handling began 1 week prior to surgery and continued for the duration of the experiment.

2.2. Surgical procedures for electrode implantation

All surgical procedures were performed stereotaxically under aseptic conditions and were in accordance with the guidelines approved by the Institutional Animal Care and Use Committee (protocol AN-14829). Animals were anesthetized with sodium pentobarbital (40 mg/kg, i.p.; Ovation Pharmaceuticals, Deerfield, IL), placed in the stereotaxic apparatus, and secured using blunt rodent ear bars as described previously [69]. The appropriate depth of anesthesia was judged by the absence of palpebral reflexes and a response to tail pinch. Core body temperature was maintained at 35 ± 1 °C with a thermostatic heating pad and a rectal thermister probe. A scalp incision was made, and the skin was retracted. The skull surface was cleaned in preparation for electrode implantation. After completion of the surgical procedure, ampicillin (50 mg per rat, s.c. Bristol-Myers Squibb, Princeton, NJ) was administered to control any potential postsurgical infection. Potential postoperative pain was controlled with buprenorphine (0.03 mg/kg, s.c.; Ben Venue Laboratories, Bedford, OH).

To record vigilance states, cortical electroencephalogram (EEG), dorsal neck muscle electromyogram (EMG) and hippocampal EEG (to record theta wave activity) recording electrodes were chronically implanted as described previously [14,18]. All electrodes were secured to the skull with dental acrylic. Electrodes were crimped to miniconnector pins and brought together in a plastic connector. Immediately after surgery, animals were placed in recovery cages and monitored for successful recovery from anesthesia and surgery. Successful recovery was gauged by the return of normal postures, voluntary movement, and grooming.

2.3. Habituation to sleep–wake recording conditions

After a postsurgical recovery period of 7–10 days, rats were habituated to a polygraphic sleep–wake recording cage under a freely moving recording conditions for 7 days as described in previous publications [15,21]. During their recovery, habituation, and free-moving recording conditions, all rats experienced the same 12-h light/dark cycle with free access to food and water. These 6-h habituation sessions (from 10:00 a.m. to 4:00 p.m.) were also considered to be the baseline recording sessions for electrode testing and monitoring daily variations in the percentages of wake/sleep stages.

2.4. Drugs

Eszopiclone (Sepracor Inc., Marlborough, MA) or zolpidem (Sigma-Aldrich Co., St. Louis, MO) were used in this study. The compounds were dissolved in 50 mM acetate buffer. Control subjects were injected with an identical vehicle. The doses of both drugs were 1, 3, and 10 mg/kg. These doses were predetermined based on previous studies to determine the effects of zopiclone, eszopiclone, and zolpidem on sleep–wake behavior in guinea pigs [110,111] and rats [34,35]. All drugs were injected i.p. in a final volume of 1.0 ml.

2.5. Contextual fear conditioning and memory testing apparatus and procedures

This apparatus is an automated freezing behavior testing chamber (30 cm × 24 cm × 21 cm; Standard modular test chamber, ENV-008; Sound attenuating cubicle, ENV-022MD; Med Associates, St. Albans, VT). The chamber is constructed from aluminum (side walls) and Plexiglas (rear wall, ceiling, and hinged front door) and is situated in a sound-attenuating cabinet located in a brightly lit and isolated room. The floor of the chamber consists of 19 stainless-steel rods (4 mm in diameter) spaced 1.5 cm apart (center-to-center). Rods are wired to a shock source and solid-state grid scrambler for the delivery of foot-shocks. A speaker is mounted outside a grating in one wall of the chamber for the delivery of acoustic stimuli (tone). One small light bulb is mounted next to the speaker in the wall of the chamber for the delivery of light stimuli. A closed circuit video camera is mounted inside on a hinged front door of the cabinet to videotape the behavior of the rat inside the chamber. A ventilation fan in the cabinet provides background noise (65 db). A 15 W house light is mounted on the ceiling of the cabinet for illumination. Stimulus presentations are controlled by a custom written computer program using MED-PC (Med Associates, St. Albans, VT). Video freeze responses

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