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R-zacopride, a 5-HT3 antagonist/5-HT4 agonist, reduces sleep apneas in rats

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Abstract

The effects of *R*-zacopride, a benzamide with potent 5-HT3 receptor antagonist and 5-HT4 receptor agonist properties, on spontaneous apneas were studied in 10 Sprague-Dawley rats by monitoring respiration and sleep for 6 h. *R*-zacopride (0.5, 1.0 and 10.0 mg/kg) suppressed spontaneous central apneas during non-rapid-eye-movement (NREM) sleep by 50% (P=.05 for 0.5 mg/kg, P=.02 for 1.0 mg/kg and P=.001 for 10.0 mg/kg dose vs. control), and during rapid-eye-movement (REM) sleep by 80% by all doses tested (P<.0007) for at least 2 h after intraperitoneal injection. We conclude that *R*-zacopride, over a 20-fold dose range, significantly reduces central apnea expression during NREM and REM sleep in the rat. The efficacy of this compound to suppress central apneas most probably arises from its antagonist actions at 5-HT3 receptors or from its mixed agonist/antagonist profile at 5-HT4/5-HT3 receptors.

Keywords: *R*-zacopride; Central sleep apneas; Rats

1. Introduction

Systemically administered serotonergic compounds have complex and poorly understood effects on the respiratory system. Although some studies suggest that activation of endogenous serotonin within the central nervous system (CNS) stimulates phrenic and upper airway motoneurons (Fenik et al., 1997; Milhorn et al., 1980), others conclude that brainstem serotonergic systems are important inhibitors of chemoreflex ventilatory patterns (cf. Martin-Body and Grundy, 1985). Administration of two selective serotonin reuptake inhibitors (SSRIs), fluoxetine (Hanzel et al., 1991) and paroxetine (Kraiczi et al., 1999), was demonstrated to benefit some, but not all, patients with sleep apnea syndrome (SAS). In contrast, injection of serotonin, which does not cross the blood–brain barrier, into the venous circulation, heart or pulmonary artery of rats, produced dose-dependent apnea (cf. Yoshioka et al., 1992), an effect mediated by 5-HT2 and 5-HT3 receptors in or on the nodose ganglia and abolished by pretreatment with 5-HT2 or 5-HT3 receptor antagonists (Yoshioka et al., 1992).

In freely moving rats, we have shown previously that intraperitoneal administration of serotonin dramatically increases the rate of spontaneous sleep-related apneas, an effect blocked by pretreatment with ondansetron (GR38032F), a selective 5-HT3 receptor antagonist (Butler et al., 1988; Carley and Radulovacki, 1999a). At higher doses, ondansetron further suppressed spontaneous central apneas (Radulovacki et al., 1998), a well-documented behavior in rats (Carley et al., 1996a,b; Christon et al., 1996; Mendelson et al., 1988; Monti et al., 1995, 1996; Radulovacki et al., 1996, 1998; Sato et al., 1990; Thomas et al., 1992, 1995). This apnea suppressant effect was particularly pronounced during rapid-eye-movement (REM) sleep, with only transient (1–2 h) reduction in apnea during non-rapid-eye-movement (NREM) sleep. Administration of remeron (the ± racemate of mirtazapine), which enhances serotonin neurotransmission at 5-HT1 receptors in the brain

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but acts as a specific antagonist at 5-HT2 and 5-HT3 receptors in the CNS and peripheral nervous system (DeBoer, 1996; DeVane, 1998), suppressed central apneas for 6 h in rats both during NREM and REM sleep (Carley and Radulovacki, 1999b).

In view of this evidence that peripheral administration of a 5-HT3 antagonist reduced spontaneous sleep apneas (Radulovacki et al., 1998) and that this effect was amplified by coactivation of CNS 5-HT1 receptors (Carley and Radulovacki, 1999b), we looked for other 5-HT3 antagonists with central 5-HT agonism. The relevant chemical classes of drugs were benzamides and benzimidazoles. We selected *R*-zacopride (Sanofi-Synthelabo), a benzamide with 5-HT3 receptor antagonist and 5-HT4 receptor agonist properties in both the peripheral (Barnes et al., 1989; Eglen et al., 1990; Wong et al., 1993) and central nervous systems (Wong et al., 1993). Following systemic administration, zacopride is up to 20 times more potent than ondansetron and maintains the ability to block 5-HT induced bradycardia for at least 6 h, compared to less than 3 h for ondansetron (Cohen et al., 1989). Thus, the aim of this study was to explore whether a more potent and long-lasting agent that produces blockade of 5-HT3 receptors combined with activation of 5-HT4 receptors would produce greater apnea suppressant effects in rats than previous compounds tested.

2. Methods

Ten adult male Sprague–Dawley rats (300 g) were maintained on a 12-h light (08:00–20:00 hours)/12-h dark (20:00–08:00 hours) cycle for 1 week, housed in individual cages and given ad libitum access to food and water. Following 1 week of adaptation, animals were subjected to surgical procedures, which will be briefly described here. All procedures and protocols conformed to the Helsinki Accords and the policies of the American Physiological Society regarding animal experimentation.

Rats were anesthetized for the implantation of cortical electrodes for electroencephalogram (EEG) recording, and neck muscle electrodes for electromyogram (EMG) recording, using a mixture of ketamine (Vetalar 100 mg/ml) and acetylpromazine (10 mg/ml) (4:1, v/v) at a volume of 1 ml/kg body weight. The surface of the skull was exposed and cleaned with a 20% solution of hydrogen peroxide followed by a solution of 95% isopropyl alcohol. Next, a dental preparation of sodium fluoride (Flura-GEL, Saslow Dental, Mt. Prospect, IL) was applied to harden the skull, and allowed to remain for 5 min. The fluoride mixture was then removed from the skull above the parietal cortex. A thin layer of Justi cement (Saslow Dental) was applied to cover the screw heads and surrounding skull to further promote the adhesion of the implant. EMG electrodes consisted of two ball-shaped wires, which were inserted into the bilateral neck musculature. All leads were soldered to a miniature connector (39F1401, Newark Electronics). Last, the entire assembly was fixed to the skull with dental cement.

After the surgery, animals were allowed a 1-week recovery period before being used in the study. Each rat was recorded on four occasions, in random order, after intraperitoneal injection (1 ml/kg) with one of the following: (1) saline (control); (2) 0.5 mg/kg *R*-zacopride; (3) 1.0 mg/kg *R*-zacopride; or (4) 10.0 mg/kg *R*-zacopride. These doses were chosen to bracket the effective dose for REM sleep apnea suppression demonstrated for ondansetron (1 mg/kg, see Radulovacki et al., 1998). Despite the expectation of zacopride's 5-HT3 antagonist potency being greater than ondansetron's (Cohen et al., 1989), we used a maximal dose of 10 mg/kg to gain confidence in demonstrating the maximal apnea-suppressant potential of *R*-zacopride. Polygraphic recordings were made from 10:00 to 16:00 hours. Recordings for an individual animal were separated by at least 3 days.

Respiration was recorded by placing each rat, unrestrained, inside a single chamber plethysmograph (PLYU-NIR/U, Buxco Electronics, Sharon, CT, dimension 6 in. wide × 10 in. long × 6 in. high) ventilated with a bias flow of fresh air at a rate of 2 l/min. A cable plugged onto the animal's connector and passed through a sealed port carried the bioelectrical activity from the head. Respiration, EEG and EMG were displayed on a video monitor and simultaneously digitized 100 times/s and stored on computer disk (Experimenter's Workbench, Datawave Technologies, Longmont, CO). Sleep and waking states were assessed using the biparietal EEG and nuchal EMG signals on 10-s epochs as described by Benington et al. (1994). This software discriminated wakefulness (W) as a high-frequency, low-amplitude EEG with a concomitant high EMG tone, NREM sleep by increased spindle and theta activity together with decreased EMG tone, and REM sleep by a low ratio of a delta-to-theta activity and an absence of EMG tone.

As in previous investigations (Carley and Radulovacki, 1999a; Christon et al., 1996; Monti et al., 1995, 1996; Radulovacki et al., 1998), sleep apneas defined as cessation of respiratory effort for at least 2.5 s were scored for each recording session, and were associated with the stage in which they occurred: NREM or REM sleep. The duration requirement of 2.5 s represented at least two "missed" breaths, and was therefore analogous to a 10-s apnea duration requirement in humans. The events detected represented central apneas because decreased ventilation associated with obstructed or occluded airways would generate an increased plethysmographic signal, rather than a pause. As in previous reports, apneas were observed to occur as pauses between breaths (spontaneous (SP) apneas) or immediately following a sigh (postsigh (PS) apneas). As in previous reports, sighs were identified as tidal volumes at least 150% greater than the overall mean tidal volume for each recording (Christon et al., 1996). Apnea index, defined

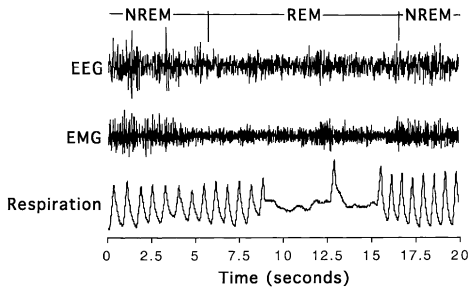

Fig. 1. Spontaneous apnea associated with onset of REM sleep. Polygraphic recording of cortical EEG (top tracing), nuchal EMG (middle tracing). Note the transition from NREM to REM sleep demarcated by appearance of lower amplitude mixed frequency EEG and loss of EMG tone beginning about 5 s into the record. This state transition is followed, after several breaths, by an apnea lasting 4 s. An isolated breath is generated and a second brief apnea ensues. The isolated breath is immediately preceded by a brief arousal identifiable by increased EMG. This REM period is aborted at 15 s with a return to NREM sleep and restored phasic respiration. These relationships between sleep states, state transitions and respiration typify the rat model of sleep related breathing disorder.

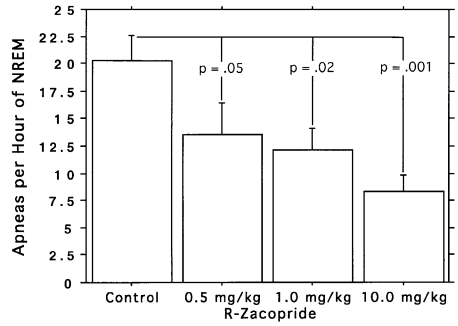

Fig. 3. Effects of *R*-zacopride on apnea expression in NREM sleep during the first 2 h after injection. NREM apnea index was significantly reduced by all three doses of *R*-zacopride. There were no statistically significant differences on NREM apnea index during the first 2 h among the three doses of *R*-zacopride tested.

as apneas per hour in a stage, were separately determined for NREM and REM sleep.

The timing and volume of each breath were scored by automatic analysis (Experimenter's Workbench, Datawave Technologies). For each animal, the mean respiratory rate (RR) and minute ventilation (MV) were computed for W throughout the 6-h control recording and used as a baseline to normalize RR and MV during sleep and during administration of drugs in that animal. The effects of sleep stage (NREM vs. REM) and injection (control vs. three active injections) on apnea indexes and respiratory pattern (rate and MV) were tested using ANOVA with repeated measures. Multiple comparisons were controlled using Fisher's protected least-significance difference (PLSD). One-way ANOVA was also performed by nonparametric (Kruskal–Wallis) analysis. Conclusions using parametric and nonparametric ANOVA were identical in all cases.

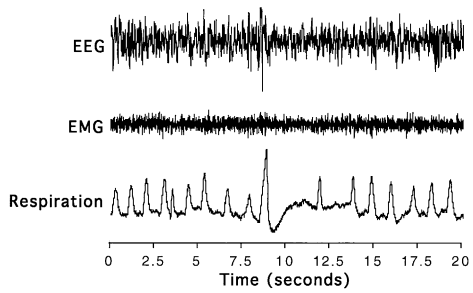

Fig. 2. Post-sigh apnea during NREM sleep. Polygraphic recording presented in the format of Fig. 1. The beginning of the record depicts phasic tidal respiration in established NREM sleep characterized by high amplitude low frequency EEG and relatively low EMG tone. At about 8.5 s, a clearly augmented breath, or sigh, occurs and is immediately followed by an expiratory apnea of several seconds duration. This respiratory pattern disturbance is not associated with any disruption in sleep state detected by EEG or EMG alteration. This is a typical presentation of postsigh apnea during slow-wave sleep. In light REM sleep, brief arousals may be accompanied by post-sigh apneas.

3. Results

Fig. 1 provides a polygraphic example of spontaneous apnea associated with the onset of REM sleep. The transition from NREM to REM sleep is demarcated by the onset of low amplitude mixed-frequency EEG activity and reduced muscle tone beginning about 5 s into the record. This state transition is followed, after several breaths, by an apnea lasting 4 s. An isolated breath is generated at 12.5 s and a second brief apnea ensues. The isolated breath is immediately preceded by a brief arousal identifiable by increased EMG. This REM period is aborted at 15 s with a return to NREM sleep and restored phasic respiration. These relationships between sleep states, state transitions and respiration typify the rat model of sleep-related breathing disorder.

Fig. 2 illustrates a postsigh apnea during stable NREM sleep. In the middle of this record, a clearly augmented breath, or sigh, is immediately followed by an apnea of several seconds in duration. This respiratory pattern disturbance is not associated with any disruption in sleep state detected by EEG or EMG alteration. This is a typical presentation of postsigh apnea during slow-wave sleep. In light NREM sleep, brief arousals may be accompanied by postsigh apneas.

Intraperitoneal administration of *R*-zacopride had no effect on mean RR, tidal volume or MV at any dose tested

Table 1
R-zacopride effects on apnea index (apneas/h) during NREM sleep

Time interval (h)	Control	*R*-zacopride 0.5 mg/kg	1.0 mg/kg	10.0 mg/kg
0–2	20±2.4	13±3.5	12±2.1	8±2.3
2–4	22.5±3.7	16±3.6	18±3.6	16±2.1
4–6	25±4.5	19±4.9	22±2.7	21±2.6

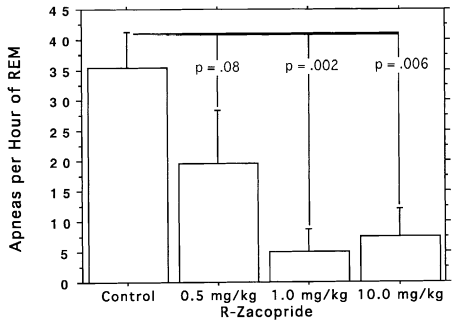

Fig. 4. Effects of *R*-zacopride on apnea expression in REM sleep during the first 2 h after injection. REM apnea index was significantly reduced by all three doses of *R*-zacopride. REM apnea index during the first 2 h was reduced to 14% of the control level by the 1.0 mg/kg dose of *R*-zacopride.

($P > .10$ for each, data not shown). This was true for both normalized and nonnormalized parameters. Furthermore, gross changes in locomotion or other behavioral effects were not evident to visual observation during the post-injection recordings.

Fig. 3 shows the effects of *R*-zacopride (0.5, 1.0 and 10.0 mg/kg) on the rate of apneas per hour of NREM sleep during the first 2 h after injection. NREM apnea index was significantly reduced by all three doses of *R*-zacopride ($P = .05$ for 0.5 mg/kg, $P = .02$ for 1.0 mg/kg and $P = .001$ for 10.0 mg/kg dose vs. control). There were no statistically significant differences in NREM apnea index among the three doses of *R*-zacopride tested. This suppression of NREM apneas by *R*-zacopride was transient, with the apnea index returning to control values after 4 h for each dose (Table 1).

Fig. 4 demonstrates the effects of *R*-zacopride (0.5, 1.0 and 10.0 mg/kg) on apnea expression in REM sleep during the first 2 h after injection. There was a significant suppressant effect of the drug on REM sleep apneas during that time period. REM apnea index was reduced by all three doses of *R*-zacopride ($P = .08$ for 0.5 mg/kg, $P = .002$ for 1.0 mg/kg and $P = .006$ for 10.0 mg/kg dose). The 1.0 and 10.0 mg/kg doses of *R*-zacopride reduced apnea index to approximately 15% of the control level. REM-sleep-related apnea was significantly reduced by *R*-zacopride by all doses tested ($P < .0007$) during the entire 6 h of polygraphic recording (Table 2), but the effect was greatest during the first 2 h for all doses tested. In fact, after administration of 1.0 mg/kg of *R*-zacopride, only a sigh apnea was observed among all 10 animals during REM sleep in Hours 0–2. Similarly, a single apnea was observed in a different animal after the 10.0 mg/kg dose.

Table 2
R-zacopride effects on apnea index (apneas/h) during REM sleep

Time interval (h)	Control	*R*-zacopride 0.5 mg/kg	1.0 mg/kg	10.0 mg/kg
0–2	36±5.2	20±7.9	5±2.2	6±4.9
2–4	33±4.1	24±8.1	16±7.2	22±8.2
4–6	35±5.4	24±5.5	10±5.1	23±7.8

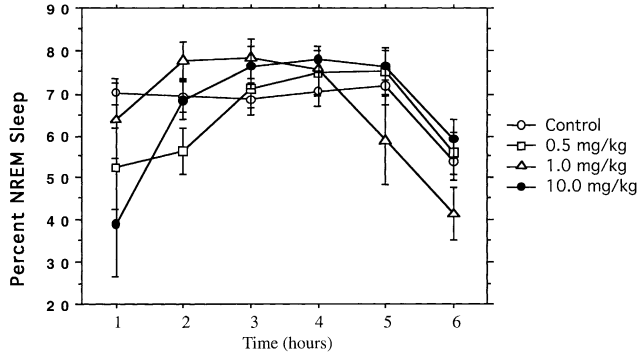

Fig. 5. Changes in percentage of recording time spent in NREM sleep for each recording hour following *R*-zacopride injection. NREM sleep expression was reduced during the first recording hour after all *R*-zacopride doses ($P < .05$ for each dose), with the greatest effect size following the highest dose. The percentage of NREM sleep was equivalent to control for all doses for Hours 3–6.

Changes in the percentage of recording time spent in NREM sleep for each recording hour following injections of three doses of *R*-zacopride are shown in Fig. 5. NREM sleep expression was reduced during the first recording hour after all *R*-zacopride doses ($P < .05$ for each dose), with the greatest effect size following the highest dose. The percentage of NREM sleep was equivalent to control for all doses for Hours 3–6.

Fig. 6 shows changes in percentage of REM sleep for each hour during the 6-h recording period following administration of three doses of *R*-zacopride. The figure shows that REM sleep was strongly suppressed by *R*-zacopride in a dose-dependent fashion. The duration of REM sleep per hour increased as each study progressed, but the REM sleep suppression by *R*-zacopride was equivalent at all time points. This REM suppression was greater for the 1.0 and

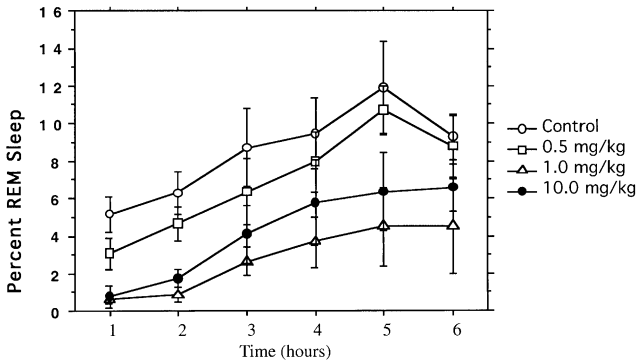

Fig. 6. Changes in percentage of recording time spent in REM sleep for each recording hour following *R*-zacopride injection. REM percent exhibited strong and independent effects of dose and time after injection. The duration of REM increased as each study progressed, but REM sleep was reduced at all time points by *R*-zacopride. This REM suppression was greater for the intermediate and high doses than for the low dose ($P < .05$ for low vs. intermediate or high).

10.0 mg/kg doses than for the 0.5 mg/kg dose ($P < .05$ for 0.5 mg/kg vs. 1.0 or 10.0 mg/kg doses).

4. Discussion

In the present study, we assessed the ability of *R*-zacopride, a combined 5-HT3 receptor antagonist and 5-HT4 receptor agonist, to affect central apneas during NREM and REM sleep in freely moving rats. The major finding of the study was that *R*-zacopride significantly reduced central apneas during NREM and during REM sleep (Figs. 3 and 4). It is of interest that degree and duration of apnea suppression were greater during REM than NREM sleep. Further, suppression of NREM apnea showed no dose dependence over the range tested, whereas REM-related apnea suppression was greater for the two higher doses vs. the lowest dose tested.

Apnea suppression was not a simple reflection of the decreased durations of NREM and REM sleep observed following injections of three doses of *R*-zacopride (Figs. 5 and 6) because apnea expression was computed as apneas per hour of NREM and REM sleep actually observed. Although statistically significant decreases were observed (Fig. 2 and Table 2), the magnitude of REM sleep apnea suppression by zacopride cannot be reliably assessed during the first 2 h because inadequate REM sleep was observed. Still clear and significant suppression of REM apneas persisted throughout the 6-h recording period.

The transient reduction in NREM sleep and persistent reduction of REM sleep (Figs. 5 and 6) produced by *R*-zacopride argues that the drug is effectively activating receptors in the CNS. From a potential pharmacotherapeutic viewpoint, suppressing REM sleep may be desirable for controlling apneas, which occur most frequently during REM sleep. Indeed, REM-suppressing antidepressants have been tested for treatment of apnea. Suppression of NREM sleep would represent an undesirable side effect. The NREM suppression observed in the present study was transient, however, lasting only 1–2 h (Fig. 5). Moreover, NREM suppression was minimal following 1.0 mg/kg of *R*-zacopride, whereas this dose was effective in suppressing NREM and REM apnea.

The relevance of apnea suppression by *R*-zacopride in the rat to pharmacotherapy of SAS in man may be questioned. It is our view that both central and obstructive apnea reflect, at least in part, dysregulation of central neural motor output patterning to the respiratory system. In humans with upper airways predisposed to collapse by anatomical, mechanical or muscular factors, this dysregulation may be manifest primarily by obstructive apneas. In humans or rats with mechanically stable upper airways, dysregulation of respiratory motor output patterning may be expressed primarily by central apneas or hypopneas.

Support for this view comes from several lines of investigation. Most patients with SAS exhibit a combination of central, mixed and obstructive apneas in a single sleep period, suggesting that any factor that destabilizes respiratory drive during sleep promotes apnea genesis. Önal and Lopata (1982) demonstrated that patients with sleep apnea exhibited obstructive apneas when breathing through their own upper airways, but central apneas when breathing through a tracheostomy. These authors concluded that obstructive apnea reflects unstable respiratory drive in individuals with upper airways predisposed to collapse by anatomical or neuromuscular defects. Furthermore, in some cases, continuous positive airwave pressure converts obstructive apneas to central apneas, again supporting the conclusion that unstable central respiratory motor patterning contributes to the pathogenesis of obstructive apnea syndrome.

If apnea reflects unstable respiratory motor patterning, interventions stabilizing respiratory drive during sleep may reduce or eliminate apnea. Indeed, inspired carbon dioxide, used to elevate respiratory drive, reduced the expression of both central (Badr et al., 1994; Skatrud and Dempsey, 1983; Steens et al., 1994) and obstructive (Badr et al., 1994; Hudgel et al., 1988) apnea in man. Similar hypercapnia in sleeping rats also reduced the rate of apnea (Christon et al., 1996). In patients, both central and obstructive apnea are most severe in REM sleep (Lugaresi et al., 1978). In the rat, central apnea is 2–10 times more frequent during REM than NREM sleep (Carley et al., 1996a,b). Essential hypertension appears to increase the risk for SAS (Fletcher et al., 1985; Lavie et al., 1984) and effective treatment of hypertension can ameliorate sleep apnea (Mayer et al., 1990). Genetic hypertension in rats is associated with a two- to fivefold increase in apnea (Carley et al., 1996b). Finally, although human data are not available, Veasey et al. (2001) have reported that ondansetron reduces obstructive apnea in the English bulldog model of sleep-related breathing disorder.

The above evidence depicts similar patterns of expression and responses to intervention for central and obstructive apnea in man and animals and central apnea in the rat. Thus, the significant *R*-zacopride-induced suppression of apnea in all sleep stages documented by the present investigation is expected to be of relevance to the mechanisms and management of human sleep-related apnea.

Suppression of REM-related apnea in the present study most likely resulted from the 5-HT3 antagonist activity of *R*-zacopride. We have previously demonstrated that ondansetron, a specific 5-HT3 antagonist, yielded powerful suppression of REM-related apneas in rats, with little impact on NREM apneas (Radulovacki et al., 1998), whereas administration of remeron, a mixed 5-HT receptor agonist/antagonist, produced equal suppression of NREM and REM-related apneas in rats (Carley and Radulovacki, 1999b). In further support of this interpretation, peripherally administered serotonin exacerbated REM-related apnea without influence on NREM apnea expression, an effect that was completely blocked by pretreatment with a low dose of ondansetron (Carley and Radulovacki, 1999a). The

fact that serotonin does not cross the blood–brain barrier argues that activity at 5-HT3 receptors in the peripheral nervous system strongly promotes REM-related apnea. On this basis, the 5-HT3 antagonist activity of *R*-zacopride in the peripheral nervous system may have contributed to the REM apnea suppression demonstrated here.

These findings, taken together, argue very strongly that there is a physiologic role for endogenous serotonergic activity in modulating sleep apneas. It is of interest that a pure 5-HT3 antagonist (ondansetron) suppressed apnea only during REM sleep, but both mirtazapine and *R*-zacopride — which combine 5-HT3 antagonism with 5-HT agonist properties — suppressed apnea with nearly equal efficacy during NREM and REM sleep. This suggests that REM apnea suppression may arise from antagonism of 5-HT3 receptors in the peripheral nervous system while NREM apnea suppression arises from 5-HT agonism at other receptor subtypes.

The location of the 5-HT4 receptors, which may yield NREM apnea suppression, cannot be identified from the present data. It seems likely that the nodose ganglia are an important target for 5-HT3 receptor antagonism accounting for REM apnea suppression. Several studies have concluded that the apnea component of the Bezold–Jarisch reflex results from the action of serotonin at the nodose ganglia in cats (Jacobs and Comroe, 1971; Sampson and Jaffe, 1975; Sutton, 1981) and rats (McQueen et al., 1998; Yoshioka et al., 1992). Intravenous administration of 5-HT or 5-HT3 agonists also stimulates pulmonary vagal receptors (McQueen et al., 1998; Yoshioka et al., 1992), which may contribute significantly to the apneic response.

In contrast, combinations of serotonin precursors and reuptake inhibitors reduced sleep-disordered respiration in the English bulldog model (Veasey et al., 1997). The rationale for using SSRIs such as fluoxetine or paroxetine to treat SAS rests on their ability to stimulate respiration and upper airway motor outputs (Hanzel et al., 1991; Kraiczi et al., 1999). Accordingly, the application of 5-HT to the floor of the fourth ventricle produced upper airway motor activation in cats (Rose et al., 1995). Moreover, a focused serotonergic intervention using buspirone, a specific 5-HT1A receptor agonist that stimulates respiration (Mendelson et al., 1990) has recently been shown to reduce apnea index by 35% in a group of five male patients with SAS (Mendelson et al., 1991). This effect of buspirone was almost identical to the NREM-specific reduction in apnea index attributed to two SSRI compounds, fluoxetine (Hanzel et al., 1991) and paroxetine (Kraiczi et al., 1999). These observations provide a likely but unconfirmed explanation for the improvements in sleep-disordered breathing observed in some patients after SSRI treatment (Hanzel et al., 1991; Kraiczi et al., 1999). Even in patients with a positive response to SSRI treatment, however, the benefit was restricted to NREM sleep, with no reduction in REM-related apneas (Hanzel et al., 1991; Kraiczi et al., 1999). Thus, it appears that drugs that enhance central serotonergic activity without ability to block peripheral 5-HT3 receptors, do not affect REM sleep-related apneas.

In summary, the present study demonstrates that *R*-zacopride significantly reduces central apnea expression during NREM and REM sleep in the rat. The efficacy of this compound in reducing central sleep apneas most probably arises from its antagonist actions at 5-HT3 receptors or from its mixed agonist/antagonist profile at 5-HT4/5-HT3 receptors. The implications of these findings for the management of SAS must be verified by appropriate clinical trials.

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