AGENTS WITH SEROTONIN-RELATED ACTIVITY FOR THE TREATMENT FOR SLEEP APNEA

STOFFE MIT SEROTONINARTIGER WIRKUNG ZUR BEHANDLUNG DER SCHLAFAPNOE

AGENTS PRESENTANT UNE ACTIVITÉ DE TYPE SEROTONINE POUR LE TRAITEMENT DES APNEES DU SOMMEIL

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• VEASEY S C ET AL: "The effects of serotonin antagonists in an animal model of sleep-disordered breathing." AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (1996 FEB) 153 (2) 776-86. , XP002111045
• RADULOVACKI M ET AL: "Serotonin 5-HT3-receptor antagonist GR 38032F suppresses sleep apneas in rats." SLEEP, (1998 MAR 15) 21 (2) 131-6. , XP002063050

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BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention generally relates to methods for the pharmacological treatment of breathing disorders and, more specifically, to the administration of agents or compositions having serotonin-related receptor activity for the alleviation of sleep apnea (central and obstructive) and other sleep-related breathing disorders.

[0002] Over the past several years much effort has been devoted to the study of a discrete group of breathing disorders that occur primarily during sleep with consequences that may persist throughout the waking hours in the form of sleepiness, thereby manifesting itself into substantial economic loss (e.g., thousands of lost man-hours) or employment safety factors (e.g., employee non-attentiveness during operation of heavy-machinery). Sleep-related breathing disorders are characterized by repetitive reduction in breathing (hypopnea), periodic cessation of breathing (apnea), or a continuous or sustained reduction in ventilation.

[0003] In general sleep apnea is defined as an intermittent cessation of airflow at the nose and mouth during sleep. By convention, apneas of at least 10 seconds in duration have been considered important, but in most individuals the apneas are 20-30 seconds in duration and may be as long as 2-3 minutes. While there is some uncertainty as to the minimum number of apneas that should be considered clinically important, by the time most individuals come to attention of the medical community they have at least 10 to 15 events per hour of sleep.

[0004] Sleep apneas have been classified into three types: central, obstructive, and mixed. In central sleep apnea the neural drive to all respiratory muscles is transiently abolished. In obstructive sleep apneas, airflow ceases despite continuing respiratory drive because of occlusion of the oropharyngeal airway. Mixed apneas, which consist of a central apnea followed by an obstructive component, are a variant of obstructive sleep apnea. The most common type of apnea is obstructive sleep apnea.

[0005] Obstructive sleep apnea syndrome (OSAS) has been identified in as many as 24 % of working adult men and 9% of similar women, with peak prevalence in the sixth decade. Habitual heavy snoring, which is an almost invariant feature of OSAS, has been described in up to 24% of middle aged men, and 14% of similarly aged women, with even greater prevalence in older subjects.

[0006] Obstructive sleep apnea syndrome’s definitive event is the occlusion of the upper airway, frequently at the level of the oropharynx. The resultant apnea generally leads to a progressive-type asphyxia until the individual is briefly aroused from the sleeping state, thereby restoring airway patency and thus restoring airflow.

[0007] An important factor that leads to the collapse of the upper airway in OSAS is the generation of a critical subatmospheric pressure during the act of inspiration that exceeds the ability of the airway dilator and abductor muscles to maintain airway stability. Sleep plays a crucial role by reducing the activity of the muscles of the upper airways including the dilator and abductor muscles.

[0008] In most individuals with OSAS the patency of the airway is also compromised structurally and is therefore predisposed to occlusion. In a minority of individuals the structural compromise is usually due to obvious anatomic abnormalities, i.e., adenotonsillar hypertrophy, retrognathia, or macroglossia. However, in the majority of individuals predisposed to OSAS, the structural abnormality is simply a subtle reduction in airway size, i.e., “pharyngeal crowding.” Obesity also frequently contributes to the reduction in size seen in the upper airways. The act of snoring, which is actually a high-frequency vibration of the palatal and pharyngeal soft tissues that results from the decrease in the size of the upper airway lumen, usually aggravates the narrowing via the production of edema in the soft tissues.

[0009] The recurrent episodes of nocturnal asphyxia and of arousal from sleep that characterize OSAS lead to a series of secondary physiologic events, which in turn give rise to the clinical complications of the syndrome. The most common manifestations are neuropsychiatric and behavioral disturbances that are thought to arise from the fragmentation of sleep and loss of slow-wave sleep induced by the recurrent arousal responses. Nocturnal cerebral hypoxia also may play an important role. The most pervasive manifestation is excessive daytime sleepiness. OSAS is now recognized as a leading cause of daytime sleepiness and has been implicated as an important risk factor for such problems as motor vehicle accidents. Other related symptoms include intellectual impairment, memory loss, personality disturbances, and impotence.

[0010] The other major manifestations are cardiorespiratory in nature and are thought to arise from the recurrent episodes of nocturnal asphyxia. Most individuals demonstrate a cyclical slowing of the heart during the apneas to 30 to 50 beats per minute, followed by tachycardia of 90 to 120 beats per minute during the ventilatory phase. A small number of individuals develop severe bradycardia with asystoles of 8 to 12 seconds in duration or dangerous tachyarrhythmias,
including unsustained ventricular tachycardia. OSAS also aggravates left ventricular failure in patients with underlying heart disease. This complication is most likely due to the combined effects of increased left ventricular afterload during each obstructive event, secondary to increased negative intrathoracic pressure, recurrent nocturnal hypoxemia, and chronically elevated sympathoadrenal activity.

[0011] Central sleep apnea is less prevalent as a syndrome than OSAS, but can be identified in a wide spectrum of patients with medical, neurological, and/or neuromuscular disorders associated with diurnal alveolar hypoventilation or periodic breathing. The definitive event in central sleep apnea is transient abolition of central drive to the ventilatory muscles. The resulting apnea leads to a primary sequence of events similar to those of OSAS. Several underlying mechanisms can result in cessation of respiratory drive during sleep. First are defects in the metabolic respiratory control system and respiratory neuromuscular apparatus. Other central sleep apnea disorders arise from transient instabilities in an otherwise intact respiratory control system.

[0012] Many healthy individuals demonstrate a small number of central apneas during sleep, particularly at sleep onset and in REM sleep. These apneas are not associated with any physiological or clinical disturbance. In individuals with clinically significant central sleep apnea, the primary sequence of events that characterize the disorder leads to prominent physiological and clinical consequences. In those individuals with central sleep apnea alveolar hypoventilation syndrome, daytime hypercapnia and hypoxemia are usually evident and the clinical picture is dominated by a history of recurrent respiratory failure, polycythemia, pulmonary hypertension, and right-sided heart failure. Complaints of sleeping poorly, morning headache, and daytime fatigue and sleepiness are also prominent. In contrast, in individuals whose central sleep apnea results from an instability in respiratory drive, the clinical picture is dominated by features related to sleep disturbance, including recurrent nocturnal awakenings, morning fatigue, and daytime sleepiness.

[0013] Currently, the most common and most effective treatment, for adults with sleep apnea and other sleep-related breathing disorders are mechanical forms of therapy that deliver positive airway pressure (PAP). Under PAP treatment, an individual wears a tight-fitting plastic mask over the nose when sleeping. The mask is attached to a compressor, which forces air into the nose creating a positive pressure within the patient’s airways. The principle of the method is that pressurizing the airways provides a mechanical "splinting" action, which prevents airway collapse and therefore, obstructive sleep apnea. Although an effective therapeutic response is observed in most patients who undergo PAP treatment, many patients cannot tolerate the apparatus or pressure and refuse treatment. Moreover, recent covert monitoring studies clearly demonstrate that long-term compliance with PAP treatment is very poor.

[0014] A variety of upper airway and craniofacial surgical procedures have been attempted for treatment of OSAS. Adenotonsillec-tomy appears to be an effective cure for OSAS in many children, but upper airway surgery is rarely curative in adult patients with OSAS. Surgical "success" is generally taken to be a 50% reduction in apnea incidence and there are no useful screening methods to identify the individuals that would benefit from the surgery versus those who would not derive a benefit.

[0015] Pharmacological treatments of several types have been attempted in patients with sleep apnea but, thus far, none have proven to be generally useful. A recent systematic review of these attempts is provided by Hudgel [J. Lab. Clin. Med., 126:13-18 (1995)]. A number of compounds have been tested because of their expected respiratory stimulant properties. These include (1) acetazolamide, a carbonic anhydrase inhibitor that produced variable improvement in individuals with primary central apneas but caused an increase in obstructive apneas, (2) medroxyprogesterone, a progestin that has demonstrated no consistent benefit in OSAS, and (3) theophylline, a compound usually used for the treatment of asthma, which may benefit patients with central apnea but appears to be of no use in adult patients with obstructive apnea.

[0016] Other attempted pharmacological treatment includes the administration of adenosine, adenosine analogs and adenosine reuptake inhibitors (U.S. Patent No. 5,075,290). Specifically, adenosine, which is a ubiquitous compound within the body and which levels are elevated in individuals with OSAS, has been shown to stimulate respiration and is somewhat effective in reducing apnea in an animal model of sleep apnea.

[0017] Other possible pharmacological treatment options for OSAS include agents that stimulate the brain activity or are opioid antagonists. Specifically, since increased cerebral spinal fluid opioid activity has been identified in OSAS, it is a logical conclusion that central stimulants or opioid antagonists would be a helpful treatment of OSAS. In reality, doxapram, which stimulates the central nervous system and carotid body chemoreceptors, was found to decrease the length of apneas but did not alter the average arterial oxygen saturation in individuals with obstructive sleep apnea. The opioid antagonist naloxone, which is known to stimulate ventilation was only slightly helpful in individuals with obstructive sleep apnea.

[0018] Because OSAS is strongly correlated with the occurrence of hypertension, agents such as angiotensin-converting enzyme (ACE) inhibitors may be of benefit in treating OSAS individuals with hypertension but this does not appear to be a viable treatment for OSAS itself.

[0019] Finally, several agents that act on neurotransmitters and neurotransmitter systems involved in respiration have been tested in individuals with OSAS. Most of these compounds have been developed as anti-depressant medications that work by increasing the activity of monoamine neurotransmitters including norepinephrine, dopamine, and serotonin.
Protriptyline, a tricyclic anti-depressant, has been tested in several small trials with variable results and frequent and significant side effects. As serotonin may promote sleep and stimulate respiration, tryptophan, a serotonin precursor and selective serotonin reuptake inhibitors have been tested in individuals with OSAS. While a patent has been issued for the use of the serotonin reuptake inhibitor, fluoxetine (U.S. Patent No. 5,356,934), initial evidence suggests that these compounds may yield measurable benefits in only approximately 50% of individuals with OSAS. Therefore in view of the fact that the only viable treatment for individuals suffering from sleep-related breathing disorders is a mechanical form of therapy (PAP) for which patient compliance is low, and that hopes for pharmacological treatments have yet to come to fruition, there remains a need for simple pharmacologically-based treatments that would offer benefits to a broad base of individuals suffering from a range of sleep-related breathing disorders. There also remains a need for a viable treatment of sleep-related breathing disorders that would lend itself to a high rate of patient compliance.

SUMMARY OF THE INVENTION

[0020] The invention is directed to providing pharmacological treatments for the prevention or amelioration of sleep-related breathing disorders.

[0021] The present invention is directed to use of a serotonin receptor antagonist, wherein the serotonin receptor antagonist is not 1-(2-fluorophenyl)-3-(4-hydroxyphenyl)-prop-2-en-1-one-O-(2-dimethylaminomethyl) oxime and its pharmaceutically acceptable salts or mirtazapine and is optionally selected from the group consisting of ondansetron (GR38032F), ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, methysergide, risperidone, cyproheptadine, clozapine, mianserin, ritanserin, and granisetron in the preparation of a medicament for preventing or ameliorating sleep-related breathing disorder.

[0022] The present invention is also directed to use of a combination of serotonin receptor antagonists for the prevention or amelioration of sleep-related breathing disorders. The combination of serotonin receptor antagonists may be directed to a single serotonin receptor subtype or to more than one serotonin receptor subtype.

[0023] The present invention is further directed to use of a combination of serotonin receptor antagonists in conjunction with a combination of serotonin receptor agonists for the prevention or amelioration of sleep-related breathing disorders. The combination of serotonin receptor antagonists as well as the combination of receptor agonist may be directed to a single serotonin receptor subtype or to more than one serotonin receptor subtype.

[0024] The present invention is also directed to use of a combination of serotonin receptor antagonists in conjunction with a α2 adrenergic receptor subtype antagonist for the prevention or amelioration of sleep-related breathing disorders. The combination of serotonin receptor antagonists may be directed to a single serotonin receptor subtype or to more than one serotonin receptor subtype.

[0025] Routes of administration for the foregoing methods may be by any systemic means including oral, intraperitoneal, subcutaneous, intravenous, intramuscular, transdermal, or by other routes of administration. Osmotic mini-pumps and timed-released pellets or other depot forms of administration may also be used. The only limitation being that the route of administration results in the ultimate delivery of the pharmacological agent to the appropriate receptor.

[0026] Sleep-related breathing disorders include, but are not limited to, obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

[0027] Exemplary serotonin receptor antagonists include, but are not limited to ondansetron (GR38032F), ketanserin, risperidone, cyproheptadine, clozapine, methysergide, granisetron, mianserin, ritanserin, cinanserin, LY-53, 857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, and other serotonin receptor antagonists.

[0028] Exemplary serotonin receptor agonists include, but are not limited to 8-OH-DPAT, sumatriptan, L694247 [2-5-[3-(4-methylsulphonyl)amino]benzyl]-1,2,4-oxadiazol-5-yl]-1H-indol-3-yl]ethanamine, buspirone, al nitidan, zalospirone, ipsapirone, gepirone, zolmitriptan, risotriptan, 311C90, α-Me-5-HT, BW723C86 (1-[5(2-thienylmethoxy)-1H-3-indolyl]propan-2-amine hydrochloride), and MCP (m-chlorophenylpiperazine).

[0029] Exemplary α2 adrenergic receptor antagonist include, but are not limited to phenoxybenzamine, phentolamine, tolazoline, terazosin, doxazosin, trimazosin, yohimbine, indoramin, ARC239, and prazosin.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] Figure 1 illustrates the effect of serotonin antagonist GR38032F (ondansetron) on the rate of apneas per hour of non-rapid eye movement (NREM) sleep as compared to control. Each data point on the figure represents the mean ± the standard error for 9 rats (p=0.007 versus control).
Figure 2 shows the effect of the serotonin antagonist GR38032F (ondansetron) on the percentage of total recording time spent in NREM sleep as compared to control. Each data point represents the mean ± the standard error for 9 rats (p=0.0001 versus control).

Figure 3 shows the effect of the serotonin antagonist GR38032F (ondansetron) on the rate of apneas per hour of rapid-eye-movement (REM) sleep as compared to control. Each data point represents the mean ± the standard error for 9 rats (p=0.01 versus control).

Figure 4 illustrates the effect of the serotonin antagonist GR38032F (ondansetron) on the percentage of total recording time spent in REM sleep as compared to control. Each data point represents the mean ± the standard error for 9 rats. Figure 5 shows the effects of the serotonin antagonist GR38032F (ondansetron) on the rate of normalized minute ventilation during wakefulness, NREM and REM sleep as compared to control. Each data bar represents the mean ± the standard error over 6 recording hours with all animals (n=9 pooled (minute ventilation was significantly larger following GR38032F administration in all behavioral states, p < 0.03 versus control).

Figure 6 shows the effects of serotonin (0.79 mg/kg), GR38032F (0.1 mg/kg)+serotonin (0.79 mg/kg), and GR38032F (0.1 mg/kg) on spontaneous apneas in NREM sleep. Each data bar represents the mean ± the standard error over 6 recording hours with all animals (n=10; p = 0.97).

Figure 7 illustrates the effects of serotonin (0.79 mg/kg), GR38032 (0.1 mg/kg) +serotonin (0.79 mg/kg), and GR38032F (0.1 mg/kg) on spontaneous apneas during REM sleep. Each data bar represents the mean ± the standard error over 6 recording hours with all animals (n=10; p = 0.01 for serotonin administration vs. control; p=0.05 for administration of GR38032F+serotonin vs. serotonin alone; p=0.99 for administration of GR38032F+serotonin vs. control; and p=0.51 for administration of GR38032F alone).

**DETAILED DESCRIPTION OF THE INVENTION**

[0031] Previous studies on the effect of serotonin or serotonin analogs on respiration in several anesthetized (see below) animal species have demonstrated variable responses. For example, administration of serotonin has been shown to cause an increase in the respiratory rate with a decrease in tidal volume in rabbits, but an increase in the tidal volume in dogs [Matsumoto, Arch. Int Pharmacodyn. Ther., 254:282-292 (1981); Armstrong et al., J. Physiol. (Lond.), 365:104 P (1985); Bisgard et al., Resp. Physiol. 37:61-80 (1979); Zucker et al. Circ. Res. 47: 509-515 (1980). In studies with cats, serotonin administration produced hyperventilation occasionally preceded by apnea [Black et al., Am. J. Physiol., 223:1097-1102 (1972); Jacobs et al., Circ. Res., 29:145-155 (1971)], or immediate apnea followed by rapid shallow breathing [Szereda-Przestaszewska et al., Respir. Physiol., 101:231-237 (1995)].


[0033] While the foregoing studies revealed significant information concerning the involvement of serotonin in the development of apneas, as stated above one significant problem with all of these studies is that the animals were anesthetized, and thus any results obtained could not be attributed to a specific serotonin agonist or antagonist, i.e., an interaction with the anesthesia or abnormal physiologic conditions associated with the anesthetic could not be ruled out.


[0035] The following examples illustrate the effects of administration of serotonin receptor antagonists, and in particular
GR38032F, to cause suppression of central apneas during non rapid eye movement (NREM) and especially during rapid eye movement (REM) sleep. This effect was associated with increased respiratory drive but did not cause cardiovascular changes at the dose tested.

The following examples also illustrate the effects of serotonin administration to induce spontaneous apnea expression, which was completely antagonized via the administration of serotonin receptor antagonists, and in particular GR38032F.

The following examples further describe the pharmacological profiles best suited for single agents or combinations of agents to successfully prevent or ameliorate sleep-related breathing disorders, i.e.,

(a) a single agent or combination of agents having either 5-hydroxytryptamine$_2$ or 5-hydroxytryptamine$_3$ receptor subtype antagonistic activity or both;

(b) a single agent or combination of agents having either 5-hydroxytryptamine$_2$ or 5-hydroxytryptamine$_3$ receptor subtype antagonistic activity or both in conjunction with either 5-hydroxytryptamine, or 5-hydroxytryptamine$_2$ receptor subtype agonistic activity or both; or

(c) a single agent or combination of agents having either 5-hydroxytryptamine$_2$ or 5-hydroxytryptamine$_3$ receptor subtype antagonistic activity or both in conjunction with a$_2$ adrenergic receptor subtype antagonistic activity.

Further aspects of the invention and embodiments will be apparent to those skilled in the art. In order that the present invention is fully understood, the following examples are provided by way of exemplification only and not by way of limitation.

Example 1 describes the preparation of the animals for treatment with either serotonin antagonists or agonists or both and subsequent physiological recording and testing.

Example 2 describes the methods for the physiological recording of treatment and control animals and results obtained from administration of a serotonin antagonist.

Example 3 describes results obtained from the administration of serotonin followed by the administration of a serotonin receptor antagonist.

Example 4 describes agents or compositions that posses a specific serotonin-related pharmacological activity that is used to effectively suppress or prevent sleep-related breathing disorders.

The following examples are illustrative of aspects of the present invention but are not to be construed as limiting.

EXAMPLE 1

Preparation of Animals for Physiological Testing and Recording

Adult, male Sprague-Dawley rats (Sasco-King, Wilmington, MA; usually 8 per test group; 300 g) were maintained on a 12-hour light (08:00-20:00 hour) / 12-hour dark (20:00-08:00 hour) cycle for one week, housed in individual cages and given ad libitum access to food and water. Following the one week of acclimatization, animals were subjected to a single agent or combination of agents having either 5-hydroxytryptamine$_2$ or 5-hydroxytryptamine$_3$ receptor subtype antagonistic activity or both.
from the bifurcation of the aorta to the renal arteries. A retractor was used to expose the contents of the abdomen and the intestine was held back using saline moistened gauze sponges. The aorta was dissected from the surrounding fat and connective tissues using sterile cotton applicators. A 3-0 silk suture was placed beneath the aorta and traction was applied to the suture to restrict the blood flow. Then the implant (TA11-PXT) was held by forceps while the aorta was punctured just cranial to the bifurcation using a 21-gauge needle bent at the beveled end. The tip of the catheter was inserted under the needle using the needle as a guide until the thin-walled BP sensor section was within the vessel. Finally, one drop of tissue adhesive (Vetbond®, 3M, Minneapolis, MN) was applied to the puncture site and covered with a small square of cellulose fiber (approximately 5 mm²) so as to seal the puncture after catheter insertion. The radio implant was attached to the abdominal wall by 3-0 silk suture, and the incision was closed in layers. After the second surgery, animals were again allowed a one week recovery period prior to administration of the serotonin receptor antagonist and subsequent physiological recording.

EXAMPLE 2

Physiological Recording and Suppression of Apneas

Physiological parameters (see below) from each animal were recorded on 2 occasions in random order, with recordings for an individual animal separated for at least 3 days. Fifteen minutes prior to each recording each animal received a systemic injection (1 ml/kg intraperitoneal bolus injection) of either saline (control) or 1 mg/kg of ondansetron (GR38032F; 1,2,3,9-tetrahydro-9-methyl-3-[[2-(methylimidazol-1-yl)methyl]carbazole-4-one; hydrochloride; Glaxo Wellcome, Inc., Research Triangle Park, NC). Polygraphic recordings were made from hours 10:00-16:00.

Respiration was recorded by placing each animal, unrestrained, inside a single chamber plethysmograph (PLYUN1R/U; Buxco Electronics, Sharon, CT; dimension 6 in. x 10 in. x 6 in.) ventilated with a bias flow of fresh room air at a rate of 2 L/min. A cable plugged onto the animal’s connector and passed through a sealed port was used to carry the bioelectrical activity from the head implant. Respiration, blood pressure, EEG activity, and EMG activity were displayed on a video monitor and simultaneously digitized 100 times per second and stored on computer disk (Experimenters’ Workbench; Datawave Technologies, Longmont, CO).

Sleep and waking states were assessed by using the biparietal EEG and nuchal EMG signals on 10-second epochs as described by Bennington et al. [Sleep, 17:28-36 (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. Sleep efficiency was measured as the percentage of total recorded epochs staged as NREM or REM sleep.

An accepted physiological animal model [rat; Monti, et al., Pharmacol. Biochem. Behav., 51:125-131 (1995)] of spontaneous sleep apnea was used to assess the effects of GR38032F. More specifically, sleep apneas, defined as cessation of respiratory effort for at least 2.5 seconds, were scored for each recording session and were associated with the stage of sleep in which they occurred: NREM or REM sleep. The duration requirement of 2.5 seconds represented at least 2 “missed” breaths, which is therefore analogous to a 10 second apnea duration requirement in humans, which also reflects 2-3 missed breaths. The events detected represent central apneas because decreased ventilation associated with obstructed or occluded airways would generate an increased plethysmographic signal, rather than a pause. An apnea index (AI), defined as apneas per hour in a stage were separately determined for NREM and REM sleep. The effects of sleep stage (NREM vs. REM) and injection (control vs. GR30832F) were tested using ANOVA with repeated measures. Multiple comparisons were controlled using Fisher’s protected least significant difference (PLSD). In addition, the timing and volume of each breath were scored by automatic analysis (Experimenters’ Workbench; Datawave Technologies, Longmont, CO). For each animal the mean respiratory rate (RR) and minute ventilation (MV) was computed for W throughout the 6 hour control recording and used as a baseline to normalize respiration during sleep and during GR38032F administration in that animal. One way ANOVA was also performed by non-parametric (Kruskal-Wallis) analysis. Conclusions using parametric and non-parametric ANOVA were identical in all cases.

Similar software (Experimenters’ Workbench; Datawave Technologies, Longmont, CO) was employed to analyze the blood pressure waveform; for each beat of each recording, systolic (SBP) and diastolic (DBP) blood pressures and pulse interval were measured. The pulse interval provided a beat by beat estimate of HP. Mean BP (MBP) was estimated according to the weighted average of SBP and DBP for each beat: MBP = DBP + (SBP-DBP)/3. The parameters for each beat were also classified according to the sleep/wake state and recording hour during which they occurred.

Results of the administration of the serotonin antagonist GR38032F on the rate of apneas per hour of NREM sleep during the 6 hours of polygraphic recording (see Figure 1) demonstrated no significant effect of treatment or time over 6 hours (two-way ANOVA). However, there was a significant suppression of apneas during the first 2 hours of recording as determined by paired t-tests (p < 0.01 for each). This respiratory effect was associated with a significant suppression of NREM sleep by the GR38032F during the first 2 hours as demonstrated in Fig. 2. The percentage of NREM sleep in 6 hour recordings was lower in GR38032F administered rats than in controls, but the decrease reached
statistical significance only during the first 2 hours of the recordings (p < 0.001).

[0049] Results further indicated a significant suppressant effect of GR38032F on REM sleep apneas throughout the 6 hour recording period (p<0.01 for drug effect on 2-way ANOVA; see Figure 3). This effect was particularly manifest during the first 4 hours of recordings, during which no animal exhibited a single spontaneous apnea in REM sleep. This effect was not a simple reflection of REM suppression during the first 4 hours.

[0050] Results set forth in Figure 4 show that GR38032F did not significantly affect REM sleep. Although REM sleep in drug treated animals was lower than in corresponding controls it did not reach statistical significance overall or during any single recording hour.

[0051] Results of the administration of GR38032F on the normalized minute ventilation during W (wake), NREM (non-rapid eye movement) sleep, and REM (rapid eye movement) sleep (see Figure 5) indicate a significant stimulation of ventilation during all behavioral states (p<0.03 for each). Finally, results indicate that GR38032F had no effect on any cardiovascular variable (MBP and HP during W, NREM, and REM sleep) measured (p>0.1 for each variable; see Table 1).

[0052] Overall these results indicate that the manipulation of serotonergic systems can exert a potent influence on the generation of central apneas in both REM and NREM sleep. Specifically the present findings indicate that systemic administration of a 5-hydroxytryptamine_{3} receptor antagonist suppresses spontaneous apnea expression; completely abolishing REM-related apnea for at least 4 hours after intraperitoneal injection. This apnea suppression was associated with a generalized respiratory stimulation that was observed as increased minute ventilation during both waking and sleep. These significant respiratory effects were observed at a dose which caused no change in heart rate or blood pressure, even during the first 2 hours, when respiration was maximal.

[0053] Those of skill in the art will recognize that exemplary serotonin receptor antagonists include, but are not limited to (a) ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, pipеразин, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, and methysergide (Research Biochemicals, Inc., Natick, MA); (b) risperidone (Janssen Pharmaceutica, Titusville, NJ); (c) cyproheptadine, clozapine, mianserin, and ritanserin (Sigma Chemical Co., St. Louis, MO); (d) granisetron (SmithKline Beecham, King of Prussia, PA); and other serotonin receptor antagonists may be used to prevent or ameliorate sleep-related breathing disorders. Further, those of skill in the art will also recognize that the results discussed above may be easily correlated to other mammals, especially primates (e.g., humans).

EXAMPLE 3

Induction and Suppression of Sleep Apneas

[0054] Administration of serotonin or serotonin analogs produced variable respiratory responses in anesthetized animals of several species (see above, DETAILED DESCRIPTION OF THE INVENTION). As shown above in Example 2, intraperitoneal administration of 1 mg/kg GR38032F, a selective 5-hydroxytryptamine_{3} receptor antagonist, suppressed spontaneous central apneas. This effect was especially prominent in REM sleep, during which apneas were completely abolished for at least 4 hours following injection. The apnea suppressant effect of GR38032F was paralleled by increased respiratory drive but BP and heart rate changes were absent at the dose tested.

[0055] Suppression of spontaneous apneas during natural sleep by GR38032F (see Example 2) is consistent with prior studies in anesthetized rats, wherein 5-hydroxytryptamine and 2-methyl-5-hydroxytryptamine, a selective 5-HT_{3} receptor agonist, provoked central apneas that were antagonized by GR38032F. Since 5-hydroxytryptamine does not penetrate the blood-brain barrier (BBB), these results (from the prior studies) indicate that stimulation of peripheral 5-hydroxytryptamine receptors, and more particularly 5-hydroxytryptamine_{3} receptors seemed to have provoked the occurrence of central apneas. In view of that study, performed in anesthetized animals, as well as our study (described in Example 2 above) in freely moving rats with respect to administration of GR38032F, we studied the ability of increased serotonergic activity at peripheral 5-hydroxytryptamine receptors, and more specifically, 5-hydroxytryptamine_{3} receptors to promote spontaneous sleep-related central apneas and whether any induction of apneas would be susceptible to antagonism by administration of 5-hydroxytryptamine receptor antagonists.
Conclusions using parametric and nonparametric ANOVA were identical in all cases. 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.

Results of the administration of either serotonin alone (0.79 mg/kg), GR38032F (0.1 mg/kg) + serotonin (0.79 mg/kg), or GR38032F alone (0.1 mg/kg) on the ability to promote spontaneous apneas in NREM sleep during a 6 hour polygraphic recording is set forth in Figure 6. Specifically, during NREM sleep, the spontaneous apnea index was not affected by any drug treatment.

As set forth in Table 2 (percentages of waking, NREM, and REM sleep during 6 hours of polygraphic recording following drug administration), intraperitoneal administration of serotonin alone, GR38032F + serotonin, or GR38032F alone had no effect on sleep architecture. Finally, no treatment group tested had a significant effect on RR, VE, mean BP, HP, or PS apnea index (data not shown).

**TABLE 2 Effects of 5-HT and GR38032F on Sleep/Wake Architecture**

<table>
<thead>
<tr>
<th></th>
<th>% Wakefulness</th>
<th>% NREM</th>
<th>% REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (saline)</td>
<td>33.7 ± 2.5*</td>
<td>58.0 ± 1.9</td>
<td>6.9 ± 1.1</td>
</tr>
<tr>
<td>5-HT (0.79 mg/kg)</td>
<td>30.2 ± 3.2</td>
<td>59.9 ± 3.3</td>
<td>6.5 ± 1.1</td>
</tr>
<tr>
<td>5-HT + GR38032F</td>
<td>36.7 ± 8.7</td>
<td>56.0 ± 7.6</td>
<td>5.3 ± 1.4</td>
</tr>
<tr>
<td>GR38032F (0.1 mg/kg)</td>
<td>28.8 ± 6.4</td>
<td>63.4 ± 5.7</td>
<td>7.3 ± 2.3</td>
</tr>
<tr>
<td>p (1-way ANOVA)</td>
<td>0.43</td>
<td>0.71</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*All values reflect means ± SE for percent recording time.

Overall these results indicate that manipulation of peripheral serotonin receptors exerts a potent influence on the generation of central apneas during REM sleep. Specifically, the present results show that systemic administration of serotonin increases spontaneous apnea expression in sleep. Although the dose of serotonin employed had no effect on sleep, cardiovascular variables, RR, or VE, the REM-related spontaneous apnea index increased > 250%. Further, it is important to note that the mechanisms of apnea genesis are at least partially sleep-state specific, as NREM apneas were unaffected.

These findings demonstrate that exogenous administration of 5-hydroxytryptamine agonists and antagonists at various doses produces changes in apnea expression that are specific to REM sleep. Such findings indicate that there is a physiologic role for endogenous serotoninergic activity in modulating the expression of apnea, especially during REM sleep. Moreover, because serotonin does not cross the blood-brain barrier, the finding that serotonin exerts a converse effect to GR38032F indicates that the relevant receptors are located in the peripheral nervous system. Further, the...
present data suggest that the action of supraphysiologic levels of serotonin on apneas is receptor mediated in that pretreatment with a low dose (0.1 mg/kg) of GR38032F, which had no independent effect on any measured parameter, including apneas, fully blocked the effects of exogenous serotonin on apnea expression.

In view of the foregoing data, the likely peripheral site of action for the observed apnea-promoting effects of serotonin administration is thought to be the nodose ganglia of the vagus nerve. More specifically, 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 et al., Circ. Res., 29:145-155 (1971), Sampson et al., Life Sci., 15:2157-2165 (1975), Sutton, Pflugers Arch., 389:181-187 (1981)] and rats [Yoshioka et al., J. Pharmacol. Exp. Ther., 260:917-924 (1992) and McQueen et al., J. Physiol., 507:843-855 (1998)]. Intravenous administration of serotonin or 5-hydroxytryptamine receptor agonists also stimulates pulmonary vagal receptors [McQueen et al., J. Physiol., 507:843-855 (1998)], which may contribute significantly to the apneic response.


The serotonin-induced Bezold-Jarisch reflex in anesthetized animals includes apnea and bradycardia. At the dose employed, serotonin did not elicit changes in either heart rate or mean BP over the 6 hour recording period. Beat-to-beat heart rate and BP variability, assessed as coefficients of variation, were also unaffected by serotonin at the dose tested. The observed dissociation of cardiovascular and respiratory responses to serotonin indicates that changes in apnea expression were not baroreceptor mediated.

Although the Bezold-Jarisch reflex in anesthetized animals and serotonin-induced apneas in REM sleep are not the same phenomenon, they may be related by similar mechanisms. When serotonin receptors are strongly manipulated by exogenous means, i.e., either with serotonergic agonists or antagonists, the expression of spontaneous apneas in REM sleep can be amplified or suppressed. However, our observation that 1 mg/kg GR38032F significantly suppressed REM apneas does not preclude a role for 5-hydroxytryptamine receptor or other 5-hydroxytryptamine receptor subtypes in the peripheral regulation of the apnea expression, and in fact the invention also contemplates the use of 5-hydroxytryptamine receptor agonists alone or in combination as well as serotonin antagonists that exhibit both type 2 and type 3 receptor antagonism (see Example 4).


Overall, the results presented herein indicate that the exacerbation of spontaneous apnea during REM sleep produced by peripherally administered serotonin is receptor mediated. Such findings also indicate a physiologic role for endogenous serotonin in the peripheral nervous system in modulating sleep apnea expression under baseline conditions.

**EXAMPLE 4**

**Suppression or Prevention of Sleep Apneas**

As indicated by the data presented herein (see Examples 2 and 3) serotonin plays an important and integral role in apnea genesis, which is both highly site and receptor subtype specific. More specifically, the efficacy of a serotonin
receptor antagonist to suppress apnea is based on its activity in the peripheral nervous system, with the nodose ganglia of the vagus nerves appearing to be a crucial target site. 5-hydroxytryptamine\textsubscript{2} and 5-hydroxytryptamine\textsubscript{3} receptors at this site are clearly implicated in serotonin-induced apnea in anesthetized animals [Yoshioka et al., J. Pharmacol. Exp. Therp., 260:917-924 (1992)]. In conjunction with these previous findings, the data presented herein (that administration of serotonin strictly to the peripheral nervous system exacerbates sleep-related apnea) indicates the importance of nodose ganglion serotonin receptors of both types in sleep apnea pathogenesis. Moreover, the serotonin-induced increase in apnea expression was completely blocked by a low dose of GR38032F, a 5-hydroxytryptamine\textsubscript{2} antagonist. Such a result indicates that the previously demonstrated suppression of apnea by GR38032F (see Example 2) most probably resulted from activity in the peripheral nervous system.

Therefore, in view of the foregoing, sleep related breathing disorders (sleep apnea syndrome, apnea of infancy, Cheyne-Stokes respiration, sleep-related hypoventilation syndromes) may be effectively prevented or suppressed via systemic administration of pharmacological agents exhibiting either serotonin type 2 or type 3 receptor antagonism, alone or in combination as well as agents that exhibit both serotonin type 2 and type 3 receptor antagonism.

Effective treatments for the prevention or suppression of sleep-related breathing disorders include systemic administration of a 5-hydroxytryptamine\textsubscript{2} or 5-hydroxytryptamine\textsubscript{3} receptor antagonist either alone or in combination. In a preferred embodiment the serotonin receptor antagonist has activity only in the peripheral nervous system and/or does not cross the blood-brain barrier. In a more preferred embodiment the serotonin receptor antagonist displays both 5-hydroxytryptamine\textsubscript{2} and 5-hydroxytryptamine\textsubscript{3} receptor subtype antagonism.

Current pharmacological treatments for sleep-related breathing disorders also involve apnea suppression via serotonin agonist effects within the central nervous system, and more specifically the brainstem. Indeed, it was in view of their potential to stimulate respiration and upper airway motor outputs that serotonin enhancing drugs were originally tested as pharmacological treatments for sleep apnea syndrome. One early report suggested that L-tryptophan, a serotonin precursor, may have a beneficial effect on sleep apnea syndrome [Schmidt, Bull. Eur. Physiol. Respir., 19:625-629 (1982)]. More recently fluoxetine [Hanzel et al., Chest., 100:416-421 (1991)] and paroxetine [Kraicz et al., Sleep, 22:61-67 (1999)], both selective serotonin reuptake inhibitors (SSRIs), were demonstrated to benefit some but not all patients with sleep apnea syndrome. In addition, combinations of serotonin precursors and reuptake inhibitors reduced sleep disordered respiration in English bulldog model of sleep apnea syndrome [Veasey et al., Sleep Res., A529; 1997 and Veasey et al., Am. J. Resp. Crit. Care Med., 157:A655 (1997)]. However, despite ongoing investigations these encouraging early results with serotonin enhancing drugs have not been reproduced.

The foregoing efforts with serotonin-enhancing drugs indicate that the potential utility of serotonin precursors or SSRIs in apnea treatment resides strictly in their central nervous system effects. Therefore, it is precisely because the serotonin enhancing effects of SSRIs in the peripheral nervous have been left unchecked that these compounds have not demonstrated reproducible effects in apnea treatment. In fact buspirone, a specific 5-hydroxytryptamine\textsubscript{1A} agonist, which stimulates respiration [Mendelson et al., Am. Rev. Respir. Dis., 141:1527-1530 (1990)], has been shown to reduce apnea index in 4 of 5 patients with sleep apnea syndrome [Mendelson et al., J. Clin. Psychopharmacol., 11:71-72 (1991)] and to eliminate post-surgical apneustic breathing in one child [Wilken et al., J. Pediatr., 130:89-94 (1997)]. Although buspirone acts systemically, 5-hydroxytryptamine, receptors in the peripheral nervous system have not been shown to play a role in apnea genesis. The modest apnea suppression induced by buspirone is a central nervous system effect that goes unopposed by serotonergic effects in the peripheral nervous system.

The rationale for using SSRIs such as fluoxetine or paroxetine to treat sleep apnea syndrome rests in part on their ability to stimulate upper airway motor outputs. Applications of serotonin to the floor of the fourth ventricle [Rose et al., Resp., Physiol., 101:59-69 (1995)] or into the hypoglossal motor nucleus [Kubin et al., Neurosci. Lett., 139:243-248 (1992)] produce upper airway motor activation in cats; effects which appear to be mediated predominantly by 5-hydroxytryptamine\textsubscript{2} receptors. Conversely, systemic administration of 5-hydroxytryptamine\textsubscript{2} receptor antagonists to English bulldogs reduces electrical activation of upper airway muscles, diminishes upper airway cross-sectional area and promotes obstructive apnea [Veasey et al., Am. J. Crit. Care Med., 153:776-786 (1996)]. These observations provide a likely explanation for the improvements in sleep-disordered breathing observed in some patients following SSRI treatment.

In conjunction with the data presented herein (Examples 2 and 3) and the foregoing observations, sleep related breathing disorders (sleep apnea syndrome, apnea of infancy, Cheyne-Stokes respiration, sleep-related hypoventilation syndromes) may be effectively prevented or suppressed via systemic administration of

(a) an agent or combinations of agents exhibiting either serotonin type 2 or type 3 receptor antagonism (either alone or in combination with one another) and/or in combination with either a 5-hydroxytryptamine\textsubscript{1} or 5-hydroxytryptamine\textsubscript{2} receptor agonist;

(b) an agent or combination of agents or agents that exhibit both serotonin type 2 and type 3 receptor antagonism in combination with either a 5-hydroxytryptamine\textsubscript{2}, or 5-hydroxytryptamine\textsubscript{3} receptor agonist; or

(c) agents that exhibit both the proper antagonistic and agonistic pharmacological profile (i.e., an agent that is both
an agonist and antagonist at the receptor subtypes set forth above).

[0078] Preferred embodiments include the following:

(a) an agent or combination of agents wherein the serotonin agonist exhibits only central serotonergic actions;
(b) an agent or combination of agents wherein the serotonin agonist exhibits only central 5-hydroxytryptamine2 actions;
(c) an agent or combination of agents wherein the serotonin antagonist exhibits only peripheral actions while the serotonin agonist exhibits only central serotonergic actions;
(d) an agent or combination of agents that have the ability to induce central nervous system serotonin release and that possess the antagonistic profile discussed above (i.e. both a 5-hydroxytryptamine2 and 5-hydroxytryptamine3 receptor antagonist); or
(e) an agent or combination of agents that have the ability to induce central nervous system serotonin release and possess only peripheral antagonistic effects;

[0079] Those of skill in the art will recognize that many serotonin receptor agonists such as, but not limited to 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetrail, sumatriptan, L694247 (2-[5-[3-(4-methylsulphonylamo)benzyl-1,2,4-oxadiazol-5-yl]-1H-indol-3-yl]ethanamine), buspirone, alnitidin, zalospirone, ipsapirone, gepirone, zolmitriptan, risa-triptan, 311C90, α-Me-5-HT, BW723C86 (1-[5(2-thienylmethoxy)-1H-3-indolyl]propan-2-amine hydrochloride), MCPP (m-chlorophenylpiperazine), as well as others may be used in conjunction with serotonin receptor antagonists to prevent or ameliorate sleep-related breathing disorders.

[0080] Pharmacological mechanisms of action other than serotonin precursors or SSRIs may also be exploited to enhance central nervous system serotonin activity. Indeed, at least one mechanism allows augmented serotonin release to be selectively targeted at the central nervous system. Specifically, antagonism of presynaptic α2 adrenergic receptors located on brainstem serotonergic neurons (heteroreceptors) enhances serotonin release. Selective 5-hydroxytryptamine2 and 5-hydroxytryptamine3 receptor antagonists have been shown to block presynaptic α2-adrenoceptors as well as postsynaptic 5-hydroxytryptamine2 and 5-hydroxytryptamine3 receptors [deBoer, J. Clin. Psychiatr., 57(4):19-25 (1996); Devane, J. Clin. Psychiatry., 59(20):85-93 (1998); and Puziantz, Am. J. Health-Syst. Pharm., 55:44-49 (1998)]. Because the affinity of such agents for central α2 receptors is 10 times higher than for peripheral α2 receptors [Puziantz, Am. J. Health-Syst. Pharm., 55:44-49 (1998)], central serotonin release is increased with minimal adrenergic side effects such as hypertension. Thus because these pharmacological agents are high affinity antagonists at 5-hydroxytryptamine2A, 5-hydroxytryptamine2C and 5-hydroxytryptamine3 receptors, the net effect is increased post-synaptic 5-hydroxytryptamine1 activity within the brain and reduced 5-hydroxytryptamine2 and 5-hydroxytryptamine3 post-synaptic activity in the central and peripheral nervous systems. Each of these pharmacological effects serve to stimulate respiration and suppress apnea.

[0081] In view of the foregoing observations, sleep related breathing disorders (sleep apnea syndrome, apnea of infancy, Cheyne-Stokes respiration, sleep-related hypoventilation syndromes) may also be effectively suppressed or prevented via systemic administration of pharmacological agents of combinations of agents having α2 adrenergic antagonist activity with either serotonin type 2 or type 3 receptor antagonist activity (either alone or in combination with one another). Preferred embodiments include:

(a) an agent or combination of agents wherein the α2 adrenergic antagonist effects are exerted centrally;
(b) an agent or combination of agents wherein the serotonin antagonist effects are exerted peripherally;
(c) an agent or combination of agents wherein the α2 adrenergic antagonist effects are exerted centrally while the serotonin antagonist effects are exerted peripherally;
(d) the agent or combination of agents comprising embodiments a-c wherein the α2 adrenergic antagonist effect is exerted presynaptically;
(e) the agent or combination of agents of embodiments comprising a-d wherein the α2 adrenergic antagonist activity is exerted selectively at presynaptic heteroreceptors on serotonergic neurons; or
(f) the agent or combination of agents comprising embodiments a-d in which the α2 adrenergic antagonist activity is exerted by an agent or combination of agents possessing the following pharmacological profile: α2 adrenergic antagonist activity with both serotonin type 2 or type 3 receptor antagonist activity.

[0082] Those of skill in the art will recognize that many α2 adrenergic receptor antagonists such as, but not limited to phenoxybenzamine, phentolamine, tolazoline, terazosin, doxazosin, trimazosin, yohimbine, indoramin, ARC239, prazosin as well as others may be used in conjunction with serotonin receptor antagonists to prevent or ameliorate sleep-related breathing disorders.

[0083] An individual diagnosed with a sleep-related breathing disorder is administered either a composition or agent
having any of the foregoing pharmacological profiles in an amount effective to prevent or suppress such disorders. The specific dose may be calculated according to such factors as body weight or body surface. Further refinement of the calculations necessary to determine the appropriate dosage for treatment of sleep-related breathing disorders is routinely made by those of ordinary skill in the art without undue experimentation. Appropriate dosages may be ascertained through use of established assays for determining dosages. Routes of administration for the foregoing methods may be by any systemic means including oral, intraperitoneal, subcutaneous, intravenous, intramuscular, transdermal, or by other routes of administration. Osmotic mini-pumps and timed-released pellets or other depot forms of administration may also be used.

Finally, those of skill in the art will recognize that with respect to the compounds discussed above, such compounds may contain a center of chirality. Thus such agents may exist as different enantiomers of enantiomeric mixtures. Use of any one enantiomer alone or contained within an enantiomeric mixture with one or more stereoisomers is contemplated by the present invention.

Claims

1. Use of a serotonin receptor antagonist, wherein the serotonin receptor antagonist is not 1-(2-fluorophenyl)-3-(4-hydroxyphenyl)-prop-2-en-1-one-O-(2-dimethylaminoethyl)oxime and its pharmaceutically acceptable salts or mirfatrazapine in the preparation of a medicament for preventing or ameliorating sleep-related breathing disorder.

2. Use according to claim 1, wherein the serotonin receptor antagonist is selected from the group consisting of ondansetron (GR38032F), ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperoxide, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, methysergide, risperidone, cyproheptadine, clozapine, mianserin, ritanserin, and granisetron in the preparation of a medicament for preventing or ameliorating sleep-related breathing disorder.

3. Use according to claim 1 or claim 2 wherein the sleep-related breathing disorder is selected from the group consisting of obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

4. Use according to any of claims 1 to 3, wherein the serotonin receptor antagonist is a 5-hydroxytryptamine_receptor subtype antagonist.

5. Use according to any of claims 1 to 3, wherein the serotonin receptor antagonist is a 5-hydroxytryptamine_receptor subtype antagonist.

6. Use according to any of claim 1 to 3, wherein the serotonin receptor antagonist is both a 5-hydroxytryptamine_receptor subtype antagonist and a 5-hydroxytryptamine_receptor subtype antagonist.

7. Use of an agent or combination of agents having both 5-hydroxytryptamine_receptor subtype antagonistic activity and 5-hydroxytryptamine_receptor subtype receptor antagonistic activity, wherein the agent or combination of agents are selected from the group consisting of ondansetron (GR38032F), ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperoxide, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, methysergide, risperidone, cyproheptadine, clozapine, mianserin, ritanserin; and granisetron in the preparation of a medicament for preventing or ameliorating sleep-related breathing disorder.

8. Use according to claim 7 wherein the sleep-related breathing disorder is selected from the group consisting of obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

9. Use according to claim 7 or claim 8 wherein the effects of the agent or combination of agents are exerted only in the peripheral nervous system.

10. A composition comprising a serotonin receptor antagonist and a serotonin receptor agonist for use in preventing or ameliorating sleep-related breathing disorders.

11. A composition according to claim 10 wherein the sleep-related breathing disorder is selected from the group consisting
of obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

12. A composition according to claim 10 or claim 11 wherein the serotonin receptor antagonist is selected from the group consisting of ondansetron (GR38032F), ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, methysergide, risperidone, cyproheptadine, clozapine, mianserin, ritanserin, and granisetron.

13. A composition according to claim 10 or claim 11 wherein the serotonin receptor agonist is selected from the group consisting of 8-OH-DPAT, sumatriptan, L694247, buspirone, alnitidan, zalospirone, ipsapirone, gepirone, zolmitriptan, risatriptan, 311C90, α-Me-5-HT, BW723C86, and MCPP.

14. A composition according to claim 10 or claim 11 wherein the serotonin receptor antagonist is a 5-hydroxytryptamine$_2$ receptor subtype antagonist.

15. A composition according to claim 10 or claim 11 wherein the serotonin receptor antagonist is a 5-hydroxytryptamine$_3$ receptor subtype antagonist.

16. A composition according to claim 10 or claim 11 wherein the serotonin receptor agonist is a 5-hydroxytryptamine$_1$, receptor subtype agonist.

17. A composition according to claim 10 or claim 11 wherein the serotonin receptor agonist is a 5-hydroxytryptamine$_2$, receptor subtype agonist.

18. A composition according to claim 10 or claim 11 wherein the effects of the serotonin receptor agonist are exerted in the central nervous system.

19. A composition according to claim 10 or claim 11 wherein the effects of the serotonin receptor antagonist are exerted in the peripheral nervous system.

20. A composition according to claim 10 or claim 11 wherein the effects of the serotonin receptor agonist are exerted in the central nervous system and wherein the effects of the serotonin receptor antagonist are exerted in the peripheral nervous system.

21. A composition according to claim 10 or claim 11 wherein the serotonin receptor antagonist exhibits both 5-hydroxytryptamine$_2$ and 5-hydroxytryptamine$_3$ receptor subtype antagonistic activity.

22. Use of an agent or combination of agents exhibiting both 5-hydroxytryptamine$_2$ and 5-hydroxytryptamine$_3$ receptor subtype antagonistic activity selected from the group consisting of ondansetron (GR38032F), ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazine, SB-206553, SDZ-205,557, 3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, methysergide, risperidone, cyproheptadine, clozapine, mianserin, ritanserin, and granisetron in the preparation of a medicament for preventing or ameliorating sleep-related breathing disorder wherein the agent or combination of agents further exhibits the ability to induce serotonin release within the central nervous system.

23. Use according to claim 22 wherein the sleep-related breathing disorder is selected from the group consisting of obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

24. Use according to claim 22 wherein the agent or combination of agents demonstrate the serotonin receptor antagonistic activity only in the peripheral nervous system.

25. A composition exhibiting α$_2$ adrenergic receptor subtype antagonism and either 5-hydroxytryptamine$_2$ or 5-hydroxytryptamine$_3$ receptor subtype antagonism or both for use in preventing or ameliorating sleep-related breathing disorders.

26. A composition according to claim 25 wherein the sleep-related breathing disorder is selected from the group consisting
of obstructive sleep apnea syndrome, apnea of prematurity, congenital central hypoventilation syndrome, obesity hypoventilation syndrome, central sleep apnea syndrome, Cheyne-Stokes respiration, and snoring.

27. A composition according to claim 25 or claim 26 wherein the composition comprises a 5-hydroxytryptamine\(_2\) or 5-hydroxytryptamine\(_3\) receptor antagonist selected from the group consisting of ondansetron (GR38032F), ketanserin, cinanserin, LY-53,857, metergoline, LY-278,584, methiothepin, p-NPPL, NAN-190, piperazin, SB-206553, SDZ-205,557,3-tropanyl-indole-3-carboxylate, 3-tropanyl-indole-3-carboxylate methiodide, methysergide, risperidone, cyproheptadine, clozapine, mianserin, ritanserin, and granisetron.

28. A composition according to claim 25 or claim 26 comprising an \(\alpha_2\) adrenergic receptor subtype antagonist selected from the group consisting of phenoxybenzamine, phentolamine, tolazoline, terazosine, doxazosin, trimazosin, yohimbine, indoramin, ARC239, and prazosin.

29. A composition according to claim 25 or claim 26 wherein the \(\alpha_2\) adrenergic antagonist effects are exerted within the central nervous system.

30. A composition according to claim 25 or claim 26 wherein the 5-hydroxytryptamine\(_2\) or 5-hydroxytryptamine\(_3\) receptor antagonist effects are exerted in the peripheral nervous system.

31. A composition according to claim 25 or claim 26 wherein the \(\alpha_2\) adrenergic antagonist effects are exerted within the central nervous system and the 5-hydroxytryptamine\(_2\) or 5-hydroxytryptamine\(_3\) receptor antagonist effects are exerted in the peripheral nervous system.

32. A composition according to claim 29, wherein the \(\alpha_2\) adrenergic antagonist effect is exerted presynaptically.

33. A composition according to claim 30 wherein the \(\alpha_2\) adrenergic antagonist effect is exerted presynaptically.

34. A composition according to claim 31 wherein the \(\alpha_2\) adrenergic antagonist effect is exerted presynaptically.

35. A composition according to claim 29 wherein the \(\alpha_2\) adrenergic antagonist effects are exerted selectively at presynaptic heteroreceptors located on serotonergic neurons.

36. A composition according to claim 30 wherein the \(\alpha_2\) adrenergic antagonist effects are exerted selectively at presynaptic heteroreceptors located on serotonergic neurons.

37. A composition according to claim 31 wherein the \(\alpha_2\) adrenergic antagonist effects are exerted selectively at presynaptic heteroreceptors located on serotonergic neurons.

Patentansprüche


2. Verwendung nach Anspruch 1, worin der Serotonin-Rezeptorantagonist aus der aus Ondansetron (GR38032F), Ketanserin, Cinanserin, LY-53,857, Metergolin, LY-278,584, Methiothepin, p-NPPL, NAN-190, Piperazin, SB-206553, SDZ-205,557,3-Tropanylindol-3-carboxylat, 3-Tropanylindol-3-carboxylatmethiodid, Methysergid, Risperidon, Cyproheptadin, Clozapin, Mianserin, Ritanserin und Granisetron bestehenden Gruppe ausgewählt ist, zur Herstellung eines Medikaments zur Prävention oder Verbesserung von schlafbezogener Atemstörung.


4. Verwendung nach einem der Ansprüche 1 bis 3, worin der Serotonin-Rezeptorantagonist ein 5-
Hydroxytryptamin₂-Rezeptorsubtypantagonist ist.

5. Verwendung nach einem der Ansprüche 1 bis 3, worin der Serotonin-Rezeptorantagonist ein 5-Hydroxytryptamin₃-Rezeptorsubtypantagonist ist.

6. Verwendung nach einem der Ansprüche 1 bis 3, worin der Serotonin-Rezeptorantagonist sowohl ein 5-Hydroxytryptamin₂-Rezeptorsubtypantagonist als auch ein 5-Hydroxytryptamin₃-Rezeptorsubtypantagonist ist.

7. Verwendung eines Mittels oder einer Kombination von Mitteln, das/die sowohl 5-Hydroxytryptamin₂-Rezeptorsubtypantagonisten-Aktivität als auch 5-Hydroxytryptamin₃-Rezeptorsubtypantagonisten-Aktivität aufweist, worin das Mittel oder die Kombination von Mitteln aus der aus Ondansetron (GR38032F), Ketanserin, Cinanserin, LY-53.857, Metergolin, LY-278.584, Methiothepin, p-NPPL, NAN-190, Piperazin, SB-206553, SDZ-205.557, 3-Tropanylindol-3-carboxylat, 3-Tropanylindol-3-carboxylatmethiodid, Methysergid, Risperidon, Cyproheptadin, Clozapin, Mianserin, Ritanserin und Granisetron bestehenden Gruppe ausgewählt, ist, zur Herstellung eines Medikaments zur Prävention oder Verbesserung von schlafbezogener Atmungsstörung.


9. Verwendung nach Anspruch 7 oder Anspruch 8, worin die Wirkungen des Mittels oder der Kombination von Mitteln nur im peripheren Nervensystem ausgeübt werden.


12. Zusammensetzung nach Anspruch 10 oder Anspruch 11, worin der Serotonin-Rezeptorantagonist aus der aus Ondansetron (GR38032F), Ketanserin, Cinanserin, LY-53.857, Metergolin, LY-278.584, Methiothepin, p-NPPL, NAN-190, Piperazin, SB-206553, SDZ-205.557, 3-Tropanylindol-3-carboxylat, 3-Tropanylindol-3-carboxylatmethiodid, Methysergid, Risperidon, Cyproheptadin, Clozapin, Mianserin, Ritanserin und Granisetron bestehenden Gruppe ausgewählt ist.


15. Zusammensetzung nach Anspruch 10 oder Anspruch 11, worin der Serotonin-Rezeptorantagonist ein 5-Hydroxytryptamin₃-Rezeptorsubtypantagonist ist.


17. Zusammensetzung nach Anspruch 10 oder Anspruch 11, worin der Serotonin-Rezeptorantagonist ein 5-Hydroxytryptamin₂-Rezeptorsubtypagonist ist.

18. Zusammensetzung nach Anspruch 10 oder Anspruch 11, worin die Wirkungen des Serotonin-Rezeptoragonisten im Zentralnervensystem ausgeübt werden.

19. Zusammensetzung nach Anspruch 10 oder Anspruch 11, worin die Wirkungen des Serotonin-Rezeptorantagonisten
im peripheren Nervensystem ausgeübt werden.


22. Verwendung eines Mittels oder einer Kombination von Mitteln, das/die sowohl 5-Hydroxytryptamin-2- als auch 5-Hydroxytryptamin-3-Rezeptorantagonisten-Aktivität aufweist, ausgewählt aus der aus Ondansetron (GR38032F), Ketanserin, Cinanserin, LY-53.857, Metergolin, LY-278.584, Methiothepin, p-NPPL, NAN-190, Pipersazin, SB-206553, SDZ-205.557, 3-Tropanylindol-3-carboxylat, 3-Tropanylindol-3-carboxylatmethiodid, Methysergid, Risperidon, Cyproheptadin, Clozapin, Mianserin, Ritanserin und Granisetron bestehenden Gruppe, zur Herstellung eines Medikaments zur Prävention oder Verbesserung von schlafbezogener Atemstörung, worin das Mittel oder die Kombination von Mitteln weiters die Fähigkeit aufweist, die Freisetzung von Serotonin innerhalb des Zentralnervensystems zu induzieren.


27. Zusammensetzung nach Anspruch 25 oder Anspruch 26, worin die Zusammensetzung einen 5-Hydroxytryptamin-2- oder 5-Hydroxytryptamin-3-Rezeptorantagonisten, ausgewählt aus der aus Ondansetron (GR38032F), Ketanserin, Cinanserin, LY-53.857, Metergolin, LY-278.584, Methiothepin, p-NPPL, NAN-190, Pipersazin, SB-206553, SDZ-205.557, 3-Tropanylindol-3-carboxylat, 3-Tropanylindol-3-carboxylatmethiodid, Methysergid, Risperidon, Cyproheptadin, Clozapin, Mianserin, Ritanserin und Granisetron bestehenden Gruppe, umfasst.


32. Zusammensetzung nach Anspruch 29, worin die Wirkung des α-2-adrenergen Antagonisten präsynaptisch ausgeübt wird.
33. Zusammensetzung nach Anspruch 30, worin die Wirkung des α₂-adrenergen Antagonisten präsynaptisch ausgeübt wird.

34. Zusammensetzung nach Anspruch 31, worin die Wirkung des α₂-adrenergen Antagonisten präsynaptisch ausgeübt wird.

35. Zusammensetzung nach Anspruch 29, worin die Wirkungen des α₂-adrenergen Antagonisten selektiv an präsynaptischen Heterorezeptoren, die an serotonen gen Neuronen angeordnet sind, ausgeübt werden.

36. Zusammensetzung nach Anspruch 30, worin die Wirkungen des α₂-adrenergen Antagonisten selektiv an präsynaptischen Heterorezeptoren, die an serotonen gen Neuronen angeordnet sind, ausgeübt werden.

37. Zusammensetzung nach Anspruch 31, worin die Wirkungen des α₂-adrenergen Antagonisten selektiv an präsynaptischen Heterorezeptoren, die an serotonen gen Neuronen angeordnet sind, ausgeübt werden.

Revendications

1. Utilisation d’un antagoniste des récepteurs de sérotonine, dans lequel l’antagoniste des récepteurs de sérotonine n’est pas le 1-(2-fluorophénol)-3(4-hydroxyphénol)-prop-2-en-1-one-O(2-diméthylaminoéthyl)oxime et ses sels pharmaceutiques ni la mirtazapine dans la préparation d’un médicament pour empêcher ou améliorer des désordres respiratoires en relation du sommeil.

2. Utilisation selon la revendication 1, dans lequel l’antagoniste des récepteurs de sérotonine est sélectionné dans le groupe se composant d’ondansetron (GR38032F), de kesanserine, de cinanserine, de LY-53,857, de métergoline, de LY-278,584, de méthiothépine, de p-NPPL, de NAN-190, de pipérazine, de SB-206553, de SDZ-205,557, de 3-tropanylindole-3-carboxylate, de 3-tropanyl-indole-3-carboxylate méthiodide, de méthysergide, de rispéridone, de cyproheptadine, de clozapine, de miansérine, de ritanserine, et de granisétron dans la préparation d’un médicament pour empêcher ou améliorer des désordres respiratoires en relation du sommeil.


5. Utilisation selon l’une quelconque des revendications 1 à 3, dans laquelle l’antagoniste des récepteurs de sérotonine est un antagoniste de sous-type des récepteurs de 5-hydroxytryptamines-3.

6. Utilisation selon l’une quelconque des revendications 1 à 3, dans laquelle l’antagoniste des récepteurs de sérotonine est à la fois un antagoniste de sous-type des récepteurs de 5-hydroxytryptamine-2 et un antagoniste de sous-type des récepteurs de 5-hydroxytryptamine-3.

7. Utilisation d’un agent ou d’une combinaison d’agents s ayant à la fois une activité antagoniste de sous-type des récepteurs de 5-hydroxytryptamine-2 et une activité antagoniste de sous-type des récepteurs de 5-hydroxytryptamine-3, où l’agent ou la combinaison d’agents est choisi à partir de groupes se composant d’ondansetron (GR38032F), de kesanserine, de cinanserine, de LY-53,857, de métergoline, de LY-278,584, de méthiothépine, de p-NPPL, de NAN-190, de pipérazine, de SB-206553, de SDZ-205,557, de 3-tropanyl-indole-3-carboxylate, de 3-tropanyl-indole-3-carboxylate méthiodide, de méthysergide, de rispéridone, de cyproheptadine, de clozapine, de miansérine, de ritanserine, et de granisétron dans la préparation d’un médicament pour empêcher ou améliorer des désordres respiratoires en relation du sommeil.

9. Utilisation selon la revendication 7 ou la revendication 8, dans laquelle les effets de l’agent ou de la combinaison d’agent s sont exercés uniquement sur le système nerveux périphérique.

10. Une composition comprenant un antagoniste des récepteurs de sérotonine et un agoniste des récepteurs de sérotonine utilisable pour empêcher ou améliorer des désordres respiratoires en relation du sommeil.


12. Une composition selon la revendication 10 ou la revendication 11, dans laquelle l’antagoniste des récepteurs de sérotonine est sélectionnée dans le groupe se composant d’ondansetron (GR38032F), de kesanserine, de cinanserine, de LY-53,857, de métrygoline, de LY-278,584, méthiothépine, de p-NPPL, de NAN-190, de pipérazine, de SB-206553, de SDZ-205,557, de 3-tropanyl-indole-3-carboxylate, de 3-tropanyl-indole-3-carboxylate méthiodide, de méthysergide, de rispéridone, de cyproheptadine, de clozapine, de miansérine, de ritanserine, et de granisétron.

13. Une composition selon la revendication 10 ou la revendication 11, dans laquelle l’agoniste des récepteurs de sérotonine est sélectionné dans le groupe se composant de 8-OH-DPAT, de sumatriptan, de L694247, de buspirone, d’alnidian, de zalospirone, d’ipsapirone, de gépironne, de zolmitriptan, de risatriptan, de 311C90, d’α-Me-5-HT, de BW723C86, et de MCPP.

14. Une composition selon la revendication 10 ou la revendication 11, dans laquelle l’agoniste des récepteurs de sérotonine est un antagoniste de sous-type des récepteurs de 5-hydroxytryptamine$_2$.

15. Une composition selon la revendication 10 ou 1 a revendication 11, dans laquelle l’antagoniste des récepteurs de sérotonine est un antagoniste de sous-type des récepteurs de 5-hydroxytryptamine$_3$.

16. Une composition selon la revendication 10 ou la revendication 11, dans laquelle l’agoniste des récepteurs de sérotonine est un agoniste de sous-type des récepteurs de 5-hydroxytryptamine$_1$.

17. Une composition selon la revendication 10 où la revendication 11, dans laquelle l’agoniste des récepteurs de sérotonine est un agoniste de sous-type des récepteurs de 5-hydroxytryptamine$_2$.

18. Une composition selon la revendication 10 ou la revendication 11, dans laquelle les effets de l’agoniste des récepteurs de sérotonine sont exercés sur le système nerveux central.

19. Une composition selon la revendication 10 ou la revendication 11, dans laquelle les effets de l’antagoniste des récepteurs de sérotonine sont exercés sur le système nerveux périphérique.

20. Une composition selon la revendication 10 ou la revendication 11, dans laquelle les effets de l’agoniste des récepteurs de sérotonine sont exercés sur le système nerveux central et dans laquelle les effets de l’antagoniste des récepteurs de sérotonine sont exercés sur le système nerveux périphérique.

21. Une composition selon la revendication 10 ou la revendication 11, dans laquelle l’antagoniste des récepteurs de sérotonine présente à la fois une activité antagoniste de sous-type des récepteurs de 5-hydroxytryptamine$_2$ et de 5-hydroxytryptamine$_3$.

22. Utilisation d’un agent et d’une combinaison d’agent s présentant à la fois une activité antagoniste de sous-type des récepteurs de 5-hydroxytryptamine$_2$ et de 5-hydroxytryptamine$_3$ sélectionné dans le groupe se composant d’ondansetron (GR38032F), de kesanserine, de cinanserine, de LY-53,857, de métrygoline, de LY-278,584, de méthiothépine, p-NPPL, de NAN-190, de pipérazine, de SB-206553, de SDZ-205,557, de 3-tropanyl-indole-3-carboxylate, de 3-tropanyl-indole-3-carboxylate méthiodide, de méthysergide, de rispéridone, de cyproheptadine, de clozapine, de miansérine, de ritanserine, et de granisétron.

23. Utilisation selon la revendication 22, dans laquelle les désordres respiratoires en relation du sommeil sont sélec-

24. Utilisation selon la revendication 22, dans laquelle le l’agent ou la combinaison d’agent s démontrent l’activité antago-nistique des récepteurs de sérotonine uniquement sur le système nerveux périphérique.

25. Une composition présentant un antagonisme de sous-type des récepteurs α₂ adrénergiques et soit un antagonisme de sous-type des récepteurs de 5-hydroxytryptamine₂ ou de 5-hydroxytryptamine₃, soit des deux, utilisables pour empêcher ou améliorer des désordres respiratoires en relation du sommeil.


27. Une composition selon la revendication 25 ou la revendication 26 dans laquelle la composition comprend un antagoniste des récepteurs de 5-hydroxytryptamine₂ ou de 5-hydroxytryptamine₃ sélectionnés dans le groupe se composant d’ondansetron (GR38032F), de kesanserine, de cinanserine, de LY-53,857, de métergoline, de LY-53,857, de SDZ-205,557, de 3-tropanyl-indole-3-carboxylate, de 3-tropanyl-indole-3-carboxylate méthiodide, de méthysergide, de rispéridone, de cyproheptadine, de clozapine, de miansérin, de ritanserine, et de granisétron.

28. Composition selon la revendication 25 ou la revendication 26 comprenant un antagoniste de sous-type des récepteurs α₂ adrénergiques sélectionné dans le groupe se composant de phénoxybenzamine, de phentolamine, de tolazoline, de térazosine, de doxazosin, de trimazosine, d’yohimbine, d’indoramine, d’ARC29 et de prazocine.

29. Une composition selon la revendication 25 ou la revendication 26, dans laquelle les effets antagonistes α₂-adrénergiques sont exercés à l’intérieur du système nerveux central.

30. Une composition selon la revendication 25 ou la revendication 26, dans laquelle les effets antagonistes des récepteurs de 5-hydroxytryptamine₂ ou de 5-hydroxytryptamine₃ sont exercés sur le système nerveux périphérique.

31. Une composition selon la revendication 25 ou la revendication 26, dans laquelle les effets antagonistes α₂-adrénergiques sont exercés sur le système nerveux central et où les effets antagonistes récepteurs de 5-hydroxytryptamine₂ ou de 5-hydroxytryptamine₃ sont exercés sur le système nerveux périphérique.

32. Une composition selon 1 a revendication 29, dans laquelle l’effet antagoniste α₂-adrénergique est exercé de manière présynaptique.

33. Une composition selon la revendication 30 dans laquelle l’effet antagoniste α₂-adrénergique est exercé de manière présynaptique.

34. Une composition selon la revendication 31, dans laquelle l’effet antagoniste α₂-adrénergique est exercé de manière présynaptique.

35. Une composition selon la revendication 29, dans laquelle les effets antagonistes α₂-adrénergiques sont exercés de manière sélective au niveau d’hétérorécepteurs présynaptiques situés sur des neurones sérotonergiques.

36. Une composition selon la revendication 30, dans laquelle les effets antagonistes α₂-adrénergiques sont exercés de manière sélective au niveau d’hétérorécepteurs présynaptiques situés sur des neurones sérotonergiques.

37. Une composition selon la revendication 31, dans laquelle les effets antagonistes α₂-adrénergiques sont exercés de manière sélective au niveau d’hétérorécepteurs présynaptiques situés sur des neurones sérotonergiques.
FIGURE 6