Effects of $5HT_3$ Receptor Antagonism by Tropisetron on the Sleep EEG and on Nocturnal Hormone Secretion

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Two dosages (5 mg and 25 mg) of the selective $5HT_3$ receptor antagonist tropisetron (ICS 205-930) were administered to healthy male controls, and the effects on the sleep EEG and nocturnal secretory activity of growth hormone (GH) and cortisol were evaluated. The lower dosage was administered to four subjects and the higher dosage to eight on 5 consecutive days, preceded and followed by 2 days of placebo treatment. After 25 mg of tropisetron, there was a slight increase in REM sleep in the first part of the sleep period, and stage 2 was decreased during the total night. In addition, plasma cortisol levels increased earlier than under placebo, and plasma GH levels were reduced in the second part of the night. Thus, only discrete effects of tropisetron upon sleep–endocrine activity were noted, making it unlikely that serotoninergic neurotransmission exerts its well-documented effects upon sleep through $5HT_3$ receptors.
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KEY WORDS: *$5HT_3$ receptor; Tropisetron; Sleep EEG; Growth hormone; Cortisol*

Research in animals and humans indicates that serotoninergic and catecholaminergic neurotransmission play an important role in regulating behavior, specifically waking and sleep. Early work by Jouvet (1967, 1972) suggested that serotoninergic neurons of brain stem raphe nuclei are responsible for inducing slow wave sleep, and that pontomesencephalic catecholamine-containing neurons are implicated in rapid eye movement (REM) sleep and in the maintenance of wakefulness. Although this hypothesis had an enormous heuristic impact, subsequent research revealed that central processes regulating sleep are much more complex (Koella 1985; Puizillout et al. 1981; Cespuglio et al., 1989), and some data were even incompatible with the view that serotoninergic stimulation produces behavioral sleep accompanied by slow waves in the neocortex (Robertson et al. 1991). However, it remained undisputed that serotoninergic neurotransmission is essential for sleep regulation in general.

Elucidation of the exact mechanisms involved required analysis of the functional role of central 5HT receptors. To date, these 5HT receptors have been divided into four classes: $5HT_1$-like, $5HT_2$, $5HT_3$ (Bradley et al. 1986), and $5HT_4$ (Dumuis et al. 1988). The $5HT_1$ receptor family can be further subdivided into six subtypes: $5HT_{1A}$ to $5HT_{1F}$ (Frazer et al. 1990, McAllister et al. 1992, Adham et al. 1993). The few studies conducted on the effects of rather specific 5HT receptor ligands on the sleep EEG indicate that $5HT_2$ receptor antagonists induce slow wave sleep in humans (Idzikowski et al. 1986; Dijk et al. 1989) and in the rat. The effect of $5HT_2$ receptor antagonists on REM sleep is less clear, as some (Sommerfeldt et al. 1987; Borbély et al. 1988; Tortella et al. 1989), but not all (Silhol et al. 1991) studies have reported suppression of REM sleep. Only a few ligands from the $5HT_1$ receptor family have been studied. A reduction in REM sleep has been ob-

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served after $5HT_{1A}$ receptor agonist treatment of rats with ipsapirone (Tissier et al. 1990), or eltoprazine (Quattrochi et al. 1992).

Among the 5HT receptors, the $5HT_3$ class is unique because unlike the other 5HT receptors, these receptors are directly coupled to a cation channel, and their electrophysiological and molecular characterization suggests that the $5HT_3$-gated ion channel is most closely related to the nonNMDA/kainate-activated glutamate channel (Hollman et al. 1989; Maricq et al. 1991).

The $5HT_3$ receptor class is of interest for future clinical applications because antagonizing this receptor is known to prevent nausea and vomiting in cancer patients undergoing chemotherapy, radiotherapy, or both, and may also have anxiolytic, antipsychotic, and memory enhancing effects (Cutler 1990).

Tropisetron (ICS 205-930) is a tool to study effects of $5HT_3$ receptor modulation on central nervous system (CNS) activity. At a cellular level, this compound was characterized as a $5HT_3$ antagonist (Richardson et al. 1985). Tropisetron binds to $5HT_3$ receptors in the human brain (Waeber et al. 1989). Preclinical experiments demonstrated the substance to be a CNS active drug. In detail, anxiolytic effects of tropisetron are suggested from experiments in mice (Onaivi and Martin 1989) and Mongolian gerbils (Cutler 1990). In rats, the compound was shown to be capable to reduce aversive properties of drug stimuli (Acquas et al. 1990). In a recent clinical trial, an anxiolytic effect of tropisetron was found in patients with generalized anxiety disorder (Lecrubier et al. 1993). The present study explores the effects of the $5HT_3$ antagonist tropisetron on sleep and sleep-associated secretion of cortisol and growth hormone (GH) in humans.

MATERIALS AND METHODS

Subjects

Twelve healthy male volunteers (aged 21 to 31 years, mean: 26.8 $\pm$ 3.0 SD) participated in the study. None of the subjects had a personal or family history of psychiatric or neurological illness. All subjects underwent a thorough psychiatric and physical examination, as well as laboratory tests including hematology, clinical chemistry, TRH test, EEG, and ECG prior to the study.

Shift workers and individuals with a history of transmeridian flights during the past six months were excluded from the study. Subjects were rejected if there was a history of abuse of drugs, alcohol, or caffeine, or if there was any drug treatment within the three months prior to the study. No intake of alcohol or coffee (apart from one cup of coffee in the morning) was allowed during the study period.

All individuals gave written, informed consent after the purpose and protocol of the study had been explained to them. The study was approved by the local ethics committee.

Procedure

Each subject spent 11 successive nights in the sleep laboratory.

The first two nights (nights -1 and 0) served as adaptation nights for the experimental conditions. Electrodes were applied between 1945 hours and 2015 hours. Lights were switched off at 2300 hours and the subjects were awakened at 0700 hours the following morning. They were not allowed to sleep outside these hours. During nights one to nine, the sleep EEG was recorded between 2300 and 0700 hours using standard methodology (Rechtschaffen and Kales 1968).

On nights minus one to two, and nights eight and nine, the subjects were given placebo orally at 2200 hours. On nights three to seven, the first four subjects received 5 mg tropisetron (ICS 205-930) and the other eight 25 mg tropisetron orally at 2200 hours.

On days two and seven, an indwelling catheter was inserted into a forearm vein at 2030 hours. The catheter was connected to a plastic tube leading through a soundproof lock into the adjoining laboratory. The catheter was kept patent by a continuous 0.9% saline drip containing 200 units of heparine/500 ml solution.

Between 2100 hours and 0700 hours blood samples were taken every 20 min for later analysis of the plasma concentrations of GH and cortisol.

Analysis of sleep EEG and hormone profiles was performed as described in detail elsewhere (Steiger et al. 1987). The area-under-the-concentration-time-course-curve was computed following the trapezoid rule.

Sleep EEG recordings were scored manually according to standard guidelines (Rechtschaffen and Kales 1968) by a technician who was blind to the study protocol. The technician's scoring of sleep EEG records was supervised by experienced sleep researchers (Christoph J. Lauer, Thomas Pollmächer). The plasma concentrations of cortisol and GH were determined by commercial radioimmunoassays. Statistical significance for the effects on sleep EEG variables was established by calculating a Friedman two-way ANOVA (placebo period one [night 1], tropisetron [means of night 3, 4, 5 and 6], placebo period two [means of night 8 and 9]). If a significant effect was proven, subsequent group by group comparisons were analyzed by the Wilcoxon rank test. To exclude potential effects of cannulation on the sleep EEG (Adam 1982; Jarrett et al. 1984), nights two and seven were excluded from this analysis. Endocrine variables before and during treatment (nights 2 and 7, respectively) were compared with the Wilcoxon rank test.

Table 1. Sleep-EEG under 25 mg Tropisetron and Placebo (n = 8)

	Placebo 1 (day 1)	Tropisetron (day 3–6)	Placebo 2 (day 8, 9)	Friedman ANOVA
Variables of the total night				
Sleep period time (min)	445.1 ± 31.7	454.9 ± 12.6	449.7 ± 23.3	NS
Total sleep time (min)	448.1 ± 25.4	456.1 ± 12.4	455.0 ± 22.7	NS
Sleep onset latency (min)	30.6 ± 31.5	14.1 ± 6.7	25.4 ± 22.5	NS
Time awake (%SPT)	1.5 ± 2.7	1.0 ± 0.9	0.7 ± 0.9	NS
Sleep stage 1 (%SPT)	6.7 ± 4.8	7.5 ± 4.1	5.2 ± 2.5	NS
Sleep stage 2 (%SPT)	55.3 ± 5.0	53.1 ± 4.7	55.8 ± 4.5	$p < 0.05$ (T < P2)
Slow wave sleep (%SPT)	11.8 ± 5.9	13.1 ± 3.8	13.7 ± 3.7	NS
REM sleep (%SPT)	22.4 ± 4.0	22.3 ± 2.5	22.8 ± 3.6	NS
REM latency (min)	70.1 ± 33.3	83.0 ± 24.8	62.3 ± 20.8	NS
REM density	2.4 ± 0.7	2.5 ± 0.8	2.6 ± 0.8	NS
Variables of night-thirds				
1st third				
Time awake (%)	13.4 ± 13.5	6.8 ± 3.2	11.0 ± 13.1	NS
Slow wave sleep (%)	22.7 ± 16.8	28.1 ± 6.8	26.3 ± 7.6	NS
REM sleep (%)	7.0 ± 2.4	14.2 ± 3.7	10.1 ± 4.2	$p < 0.05$ (P1, P2 < T)
REM density	2.4 ± 1.8	1.9 ± 0.9	2.0 ± 1.0	NS
2nd third				
Time awake (%)	0.8 ± 1.6	1.2 ± 1.5	0.2 ± 0.3	NS
Slow wave sleep (%)	9.2 ± 6.9	8.0 ± 3.5	10.8 ± 6.3	NS
REM sleep (%)	28.5 ± 10.5	25.7 ± 4.9	22.5 ± 8.2	NS
REM density	2.4 ± 0.7	2.6 ± 1.0	2.3 ± 0.9	NS
3rd third				
Time awake (%)	5.1 ± 12.0	1.6 ± 0.8	0.2 ± 0.3	NS
Slow wave sleep (%)	1.6 ± 2.2	2.0 ± 1.7	1.4 ± 2.6	NS
REM sleep (%)	27.4 ± 9.4	29.9 ± 4.5	31.9 ± 4.9	NS
REM density	2.4 ± 0.7	2.6 ± 0.8	2.8 ± 0.9	NS

Abbreviations: P1 = Placebo 1; P2 = Placebo 2; ANOVA = analysis of variance; NS = nonsignificant; T = active treatment with 25 mg Tropisetron (day 3–6)
Numerical entries in columns two through four are mean ± SD.

RESULTS

Sleep EGG

Effects of 5 mg Tropisetron. None of the conventional sleep variables showed any systematic change under 5 mg tropisetron compared to placebo. (Data not shown.)

Effects of 25 mg Tropisetron. The sleep EEG variables before, during, and after treatment with the substance are given in Table 1. REM sleep in the first third of the night was slightly, but significantly increased under the drug. There was a slight increase in stage 2 sleep after withdrawal of 25 mg tropisetron. No other statistically significant effects on sleep–EEG variables were noted.

We reevaluated our data by visual inspection regarding possible transient effects of the drug and a possible compensatory rebound phenomenon after withdrawal, however, there were no hints detectable for such phenomena (Figure 1).

Endocrine Variables

Effects of 5 mg Tropisetron. No systematic changes in the secretion of plasma cortisol or GH were detectable under 5 mg tropisetron. (Data not shown.)

Effects of 25 mg Tropisetron. Table 2 summarizes the endocrine variables before and under active medication. The latency between "lights off" at 2300 hours and the cortisol rise (Steiger et al. 1987) was shortened under 25 mg tropisetron ($p < .05$). The GH concentration during the second half of the night was reduced ($p < .05$). No other significant differences between placebo and 25 mg tropisetron were observed.

Side-effects

In general, the substance was well tolerated. Constipation was reported by eight subjects while taking tropisetron (three subjects on 5 mg and five on 25 mg). The effect disappeared after discontinuation of the drug. No clinically significant changes in laboratory values were detected.

DISCUSSION

This study failed to document a profound effect of $5HT_3$ receptors in regulation of human sleep. In a recent study (Lecrubier et al. 1993), a statistically sig-

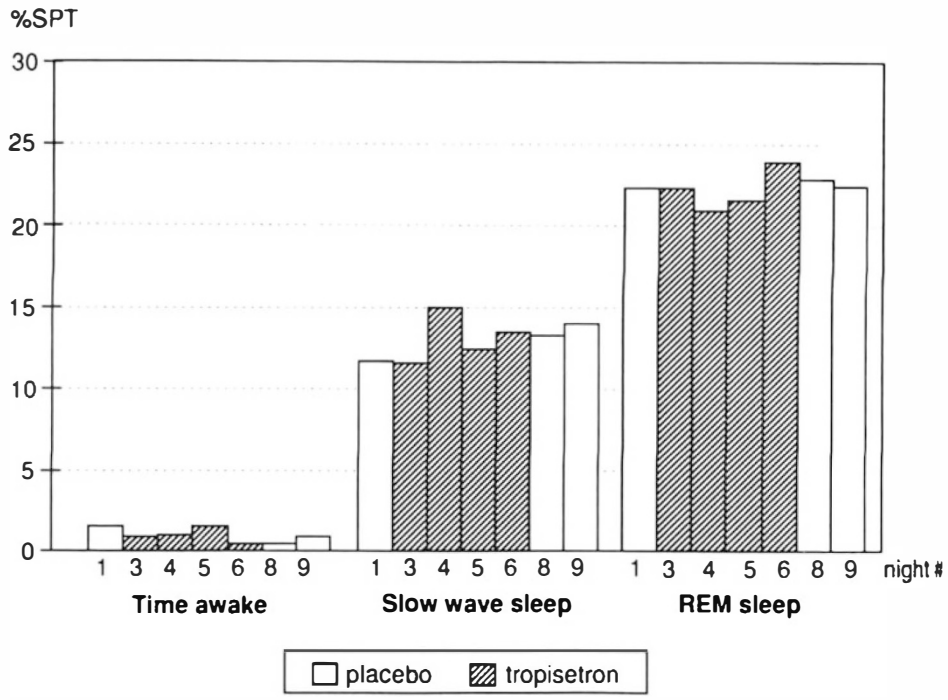

Figure 1. The course of several selected EEG sleep parameters during placebo period 1, the treatment with tropisetron (nights 3, 4, 5, 6), and the placebo period 2 (nights 8, 9) in eight healthy men.

Table 2. Endocrine Variables under 25 mg Tropisetron and Placebo (n = 8)

Period	Placebo (day 2)	25 mg Tropisetron (day 7)	Wilcoxon Rank-test
Cortisol secretion			
Mean cortisol concentration (ng/ml)			
2100–0700 hours	52.0 ± 24.0	52.2 ± 21.1	NS
2200–0300 hours	22.0 ± 25.1	19.0 ± 16.3	NS
0300–0700 hours	86.7 ± 15.2	90.5 ± 21.5	NS
Area under curve (ng/ml × min)			
2100–0700 hours	30,104 ± 13,912	31,036 ± 12,134	NS
2200–0300 hours	6,663 ± 6,701	5,423 ± 4,272	NS
0300–0700 hours	20,461 ± 4,181	22,469 ± 5,471	NS
Nadir 1 (ng/ml)	7.2 ± 7.4	6.7 ± 3.9	NS
Peak 1 (ng/ml)	66.7 ± 53.9	52.5 ± 45.8	NS
Nadir 2 (ng/ml)	32.3 ± 31.5	25.4 ± 29.9	NS
Latency			
2300 hour-cortisol rise (min)	200.0 ± 65.3	168.6 ± 57.6	$p < 0.05$
GH secretion			
Mean GH concentration (ng/ml)			
2100–0700 hours	3.9 ± 2.0	3.1 ± 1.1	NS
2200–0300 hours	4.8 ± 2.1	4.4 ± 2.1	NS
0300–0700 hours	2.3 ± 2.8	1.1 ± 0.4	NS
Area under curve (ng/ml × min)			
2100–0700 hours	2,258 ± 1,083	1,789 ± 640	NS
2200–0300 hours	1,425 ± 672	1,312 ± 618	NS
0300–0700 hours	396 ± 301	248 ± 73	$p < 0.05$
Peak	1,436 ± 601	1,301 ± 714	NS
Maximum (ng/ml)	19.3 ± 9.8	14.6 ± 9.3	NS
Latency			
Sleep-onset maximum (min)	13.4 ± 111.7	39.1 ± 62.7	NS
2300 hour-maximum (min)	42.9 ± 99.6	60.0 ± 58.9	NS
No. of secretory pulses	2.3 ± 1.0	1.9 ± 0.7	NS

nificant dose-related anxiolytic effect of tropisetron (0.5 mg/day, 5 mg/day and 25 mg/day) had been found in men after seven days. A sleep-regulatory CNS effect of the substance should be detectable within the same period of time.

Similar to our findings, in a previous study in rats, no major sleep EEG findings by $5HT_3$ receptor antagonists were found (Adrien et al. 1992). The only changes were that the higher (25 mg) dose of tropisetron slightly reduced stage 2 during the entire night and increased REM sleep during the first third of the night, whereas the amount of REM sleep of the entire night, on average, remained stable. The latter finding correlates with the report by Tissier et al. (1990) that showed an increase in REM sleep during the first two hours after administration of the 5 HT_3 antagonist ondansetron in rats.

Furthermore, the effects of $5HT_3$ receptor antagonists on nocturnal secretion of cortisol and GH were not pronounced. Plasma cortisol concentrations began to increase earlier under 25 mg tropisetron than under 5 mg or placebo. Such a reduced latency of nocturnal cortisol surge is a characteristic phenomenon in depression (Steiger et al. 1989), where altered serotoninergic neurotransmission is subject to etiological and therapeutic considerations. Plasma GH concentration during the second half of the night was reduced under a dosage of 25 mg tropisetron. It is unclear if this was a direct effect of the drug because the major secretory activity of somatotrophic cells, regularly occurring after sleep onset, remained unaffected by tropisetron.

In contrast to the 5HT antagonist used here, other 5HT receptor ligands are quite effective modulators of endocrine activity: For example, the $5HT_{1A}$ antagonists ipsapirone, gepirone, and buspirone elevate plasma ACTH and cortisol concentrations (Gilbert et al. 1988; Lesch et al. 1989; Lesch et al. 1990; Walsh et al. 1991) whereas the $5HT_{1D}$ receptor sumatriptan fails to affect pituitary-adrenocortical activity, but profoundly stimulates GH secretion (Rolandi et al. 1992). The effects of $5HT_2$ receptors in mediating endocrine activity are less documented, and only indirect evidence exists that the activation results in ACTH release (Plotsky et al. 1989).

All endocrine data were gathered from studies in the waking state. Caution is therefore warranted in any comparisons with our data because the endogenous hormone secretion is different during sleep (Steiger et al. 1987). Within these limitations, we conclude that the $5HT_3$ receptor antagonist tropisetron has no substantial effect on physiological sleep-EEG changes and nocturnal secretion of GH and cortisol. These findings need amplification by further analysis of $5HT_3$ receptor selectivity of tropisetron (i.e., binding to $5HT_3$ receptor subtypes, or $5HT_4$ receptor binding and characterization of the endocrine profile of this compound in the waking state).

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