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PHARMACODYNAMICS

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Effect of clonidine and yohimbine on sleep in healthy men: a double-blind, randomized, controlled trial

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Abstract *Objective*: To study the acute effect of clonidine, an α_2-adrenoceptor agonist, and yohimbine, an α_2-adrenoceptor antagonist, on nocturnal sleep in healthy men.
Setting: McGuire Veteran Affairs Medical Center, Richmond, Virginia, USA.
Subjects: Eight healthy male volunteers.
Methods: Each subject slept in the sleep laboratory for 2 consecutive nights on three separate sessions, at 3-week intervals. On the 2nd night of each session, the subjects received yohimbine (5.4 mg), clonidine (0.1 mg), or placebo in a double-blind, randomized, placebo-controlled, crossover design.
Results: There were no apparent effects of yohimbine. In contrast, clonidine completely suppressed rapid eye movement (REM) sleep in one subject and reduced REM sleep in the remaining seven subjects.
Conclusion: Our study confirms that clonidine markedly decreases REM, even at a low single dose, and supports the hypothesis of the important role of α_2-receptors in controlling REM sleep.

Key words REM sleep, Clonidine, Yohimbine; α_2-adrenoceptors, man

Introduction

Animal models have shown an effect of α_2-adrenoceptor stimulation and blockade on sleep. In rats, clonidine, an α_2-receptor agonist, induces sedation and sleep. Yohimbine, an α_2-receptor antagonist, produces the opposite effect: arousal and increased locomotor activity [1]. In cats, clonidine suppresses rapid eye movement (REM) sleep, and this effect is antagonized by yohimbine [2, 3]. There are limited data on the effects of clonidine and yohimbine on human sleep. Clonidine decreases REM sleep in young adults [4–8], whereas conflicting data have been reported on yohimbine [4, 6]. We studied the effect of clonidine and yohimbine on objective sleep parameters after oral single-dose administration. We expected clonidine to decrease REM sleep while increasing non-REM sleep and yohimbine to have the opposite effects.

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Methods

The protocol was approved by the Veteran Affairs Medical Center Research and Development Committee and the Virginia Commonwealth University Committee on the Conduct of Human Research. The subjects were eight healthy male volunteers, mean age 35 (8) years (range 23–46 years) and mean weight 76 (12) kg (range 61–98 kg). Each provided informed consent and was paid for his participation in the study. They ingested no medications, did not smoke, were total abstainers of alcohol, had no acute or chronic illness, had no sleeping difficulties, and their weight was within ± 25% of ideal body weight. Health status was assessed by history, physical examination and screening blood tests.

Each subject slept in the sleep laboratory for 2 consecutive nights on three separate sessions, at 3-week intervals. During each session, the 1st night was for adaptation. On the 2nd night, at 2300 hours, the subjects received either: (a) yohimbine 5.4 mg (Pegasus, USA), (b) clonidine 0.1 mg (Purepac Pharmaceutical, USA), or (c) placebo, in identical-appearing capsules. The treatment was given in a double-blind, randomized, crossover design. The subjects also participated in a study of the effect of clonidine and yohimbine on luteinizing hormone, testosterone secretion, and nocturnal penile tumescence; therefore, an indwelling catheter was placed in one forearm to collect blood samples every 10 min while subjects slept. It has been shown that intravenous blood sampling via a catheter does not induce significant disruption of sleep [9]. Blood pressure measurements were not obtained so as not to disturb sleep. The subjects were allowed to sleep ad libitum between 2300 and 0630 hours. Recordings included electroencephalogram, electro-oculogram, electrocardiogram, and nocturnal penile tumescence. During the first adaptation night, we also assessed nasal/oral airflow, abdominal and thoracic respiratory effort, transcutaneous oximetry, and electromyography to rule out sleep breathing disorders and nocturnal myoclonus. Sleep stages were scored according to the Rechtschaffen and Kales criteria. We determined the following sleep

variables: total recording time, total sleep time (TST), sleep latency, sleep stages expressed as a percentage of TST, and REM latency.

Data were analysed using Systat (Systat Inc., Evanston, IL). Because not all the variables approximated normality, the effect of yohimbine, clonidine, and placebo on the sleep variables was compared using the Friedman two-way analysis of variance. If a significant difference was found, follow-up pairwise comparisons (placebo vs clonidine and placebo vs yohimbine) were made using the Bonferroni-adjusted Wilcoxon's signed rank test. We used an overall significance level of 0.05.

Results

The only significant difference among the three treatment groups was on REM sleep ($P = 0.009$); there was a trend for a difference in stage 2 sleep ($P = 0.072$) and REM latency ($P = 0.066$). Compared to placebo, clonidine reduced REM sleep [17 (10)% vs 6 (5)%, $P = 0.012$ (Table 1)] and completely suppressed it in one subject (Fig. 1). Yohimbine had no significant effect on REM sleep.

Discussion

The imidazoline clonidine is a selective α_2-adrenoceptor agonist, is lipophilic, rapidly penetrates the brain, and its effects are primarily central [10]. Clonidine also has a small effect on serotonin but this effect seems to be indirect and mediated by noradrenergic neurons [11, 12]. High doses are associated with a less hypotensive effect, probably because it loses some of its selectivity and stimulates peripheral α_1-adrenoceptors [13].

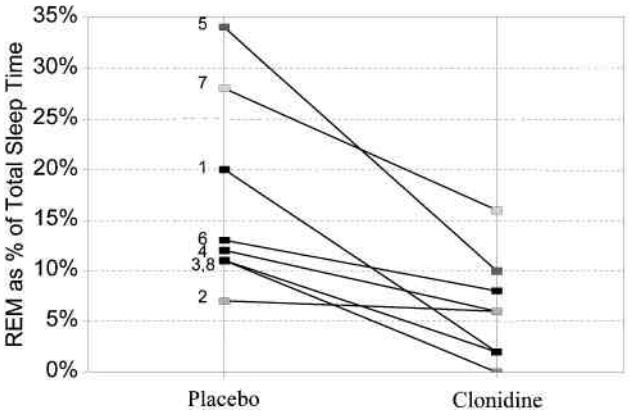

Fig. 1 Effect of clonidine on REM sleep. Subjects are numbered from lightest to heaviest weight, with subject number 1 being 61 kg and subject number 8 being 98 kg

Previous studies in healthy men have shown that clonidine has a monophasic effect on REM sleep, with a consistent decrease of REM sleep at doses between 0.1 and 0.3 mg, while the effect on other sleep stages has been variable. Clonidine, at a dose of 0.05 mg, had no effect on sleep [8]; a dose of 0.1 and 0.15 mg, only decreased REM [7] or also increased stage 2 sleep [8]; a larger dose, 0.225 to 0.3 mg, decreased REM sleep and increased stage 2 [7] or slow-wave sleep (SWS) [6]. In the studies of Gaillard et al. [5,14], the dose of clonidine was based on the subjects' weight. For comparison, we calculated that our dose of 0.1 mg corresponded to 1.4 (0.2) $\mu g \cdot kg^{-1}$ body weight (range 1–1.6 $\mu g \cdot kg^{-1}$). Doses smaller than ours, 0.2, 0.4, and 0.8 $\mu g \cdot kg^{-1}$, had no effect on REM sleep, while 0.8 $\mu g \cdot kg^{-1}$ significantly depressed stage 4 sleep; although 0.4 $\mu g \cdot kg^{-1}$ did not affect REM sleep directly, it prevented the increase of REM sleep produced by a small dose of the neuroleptic chlorpromazine [5]. In another study from the same group, 0.4 $\mu g \cdot kg^{-1}$ of clonidine decreased REM sleep in 4 out of 16 subjects; in the remaining 12 subjects it did not affect REM sleep but caused REM rebound during the following placebo night [14].The authors speculated that this rebound without previous debt could be due to desensitization of α_2-receptors by clonidine. A dose similar to ours, 1.6 $\mu g \cdot kg^{-1}$, decreased REM sleep and increased stage 2 sleep [5]. The results of our double-blind, placebo-controlled study confirm that a relatively low dose of clonidine (0.1 mg) is a potent REM sleep depressant, while it may have no effect on other sleep stages.

Yohimbine is a relatively selective α_2-receptor antagonist. Its action is both peripheral and central and its selectivity varies with the tissue studied. Radioligand-binding studies have demonstrated that it has sixfold (liver and brain) to 140-fold (uterus and lung) higher sensitivity for the α_2-than for the α_1-receptors [15]. At high concentrations it also stimulates serotonin receptors [15, 16]. Because of its activity as an α_2-antagonist, it would be expected to have the opposite effect of cloni-

Table 1 Effect of clonidine and yohimbine on sleep parameters. $n = 8$ except for REM latency, where $n = 7$ as one subject had no REM sleep during the clonidine night

	Yohimbine Mean (SD)	Clonidine Mean (SD)	Placebo Mean (SD)
Total recording time (min)	401 (28)	387 (35)	381 (25)
Total sleep time (min)	287 (99)	325 (31)	310 (48)
Sleep latency (min)	36 (52)	20 (21)	21 (24)
Sleep efficiency (%)	72 (27)	85 (11)	82 (13)
Stage I (%)	16 (10)	12 (8)	12 (6)
Stage II (%)	54 (9)	66 (13)	56 (9)
Stage III and IV (%)	16 (11)	16 (10)	15 (10)
REM (%)	15 (8)	6 (5)*	17 (10)
REM latency (min)	122 (63)	191 (88)	107 (69)

*$P = 0.012$ between clonidine and placebo

dine, and increase REM sleep. In rats, yohimbine had a biphasic effect; in low doses it increased paradoxical sleep, while very high doses depressed it, probably secondary to an effect on α_1-receptors at high doses [17].

We found that a small dose of yohimbine had no effect on sleep parameters. This result is consistent with the results of Autret et al. [4], who showed that yohimbine (10 mg) did not affect sleep in man, although it decreased the effect of clonidine when the two medications were given together. In the study of Kanno et al. [6], yohimbine 15 mg increased REM sleep and stage 1 sleep at the expense of SWS. This study was flawed by the inappropriate use of Student's *t*-test to compare more than two groups, making the results questionable. A more selective α_2-receptor antagonist, idazoxan, increased REM sleep in cats [18], but decreased REM in six healthy men [8]. Although the effect of α_2-receptor antagonists on human sleep is controversial, both in man [4] and in cats [2, 3], yohimbine antagonizes the REM-suppressive effect of clonidine, supporting the hypothesis that the α_2-receptors have an important role in the modulation of REM sleep. The lack of effect of a small dose of yohimbine given alone could be due to an insufficient CSF level. In animals, the α_2-receptor antagonists were given directly into the CNS, while we gave yohimbine orally, and there is evidence that its action on peripheral α_2-receptors is greater than on central α_2-receptors [19]. Furthermore, to detect a small effect of yohimbine, a larger sample might be necessary.

Finally, it should be noted that both clonidine and the α_2-receptor antagonists idazoxan and yohimbine also bind nonadrenergic imidazoline receptors in the brainstem [20–23]. These receptors are important for the regulation of blood pressure but probably not for the control of wakefulness. In fact, compared to clonidine, the oxazoline rilmenidine has 2–3 times higher selectivity for the imidazoline receptors, has the same antihypertensive efficacy but is less sedating [8, 23, 24]. Studies using α_2-agonists/antagonists that do not bind imidazoline receptors are needed to confirm that the effect of clonidine on REM is mediated by the α_2-receptor and not by the imidazoline receptors.

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