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Inhibition of REM sleep by ipsapirone, A 5HT1$_A$ agonist, in normal volunteers

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Abstract. In order to test the hypothesis that serotonergic mechanisms inhibit REM sleep via a 5HT1$_A$ receptor, we administered placebo and ipsapirone (10 and 20 mg by mouth 15 min before bedtime) to ten normal volunteers in a double blind fashion. Ipsapirone is a relatively selective 5HT1$_A$ receptor agonist. As predicted, ipsapirone prolonged REM latency and Mean Latency to Eye Movements (M-LEM), a measure of time between onset of REM sleep and the first eye movement of the REM period, and REM% at both doses compared with placebo. It also reduced sleep efficiency and total REM sleep time at the highest dose. These results support the hypothesis that systemic stimulation of 5HT1$_A$ receptors prolong REM latency and inhibit REM sleep.

Key words: Serotonin – 5HT1$_A$ receptors – Ipsapirone – Sleep – REM sleep – Normal volunteers

The role of serotonin in the physiology of sleep is complex and incompletely understood. Serotonin was once proposed as "the sleep transmitter" (Jouvet 1972) on the basis of the short-term insomnia following acute lesions of the serotonergic dorsal raphe nuclei and pharmacological depletion of serotonin by administration of the tryptophan hydroxylase inhibitor, *p*-chlorophenylanine. Nevertheless, chronic studies revealed a gradual return to near normal total sleep time despite chronic loss of serotonergic neurons or reduction of brain serotonin levels. It has also been hypothesized that serotonergic neurons inhibit REM sleep or at least phasic events associated with REM sleep such as pontine geniculate occipital waves ("PGO spikes") (McGinty et al. 1973; McGinty and Drucker-Colin 1982). As suggested by the reciprocal interaction hypothesis, REM sleep is promoted by cholinergic neurons and inhibited by noradrenergic and serotonergic neurons (Hobson et al. 1975).

Of considerable relevance to the reciprocal interaction hypothesis is the recent report that cholinergic low-threshold burst cells in the lateral dorsal tegmental nucleus (LDT), cholinergic neurons implicated in the generation of REM sleep and PGO waves, are inhibited by serotonin, specifically mediated by 5HT1$_A$ receptors in the in vitro brainstem slice preparation (Luebke et al. 1992). Consistent with this observation, the 5HT1$_A$ agonist, 8-OH-DPAT, inhibits REM sleep whether administered directly into the LDT in cat (Sanford et al. 1992) or systemically (Dugovic et al. 1989). Similarly, REM inhibition also follows systemic administration of other 5HT1$_A$ agonists, such as eltoprazine (Quattrochi et al. 1993), *m*-chlorophylpiperzine (m-CPP) (Sanford et al. 1992), buspirone (Lerman et al. 1986), or ipsapirone (Tissier et al. 1994) in animals, or m-CPP (Lawlor et al. 1991) and buspirone (Seidel et al. 1985) in humans.

In this paper, we present the first study in humans, to our knowledge, to test the hypothesis that ipsapirone, an orally active 5HT1$_A$ agonist, inhibits REM sleep in a dose dependent fashion. Ipsapirone is an orally active agonist at central 5HT1$_A$ receptors (Heller et al. 1990; Stahl et al. 1993) which is currently under clinical investigation in the United States as an antidepressant and anxyiolotic medication (Bertolucci et al. 1987). The dependent measures included not only REM sleep and REM latency (the time between the onset of sleep and the first REM period) but a novel measure called Mean Latency to Eye Movements (M-LEM) (the time between onset of REM sleep and the first rapid eye movement). M-LEM was first reported in 1986 and was found to be significantly shorter in bipolar depressed patients than in normal controls (Jernajczyk 1986). We have recently replicated this finding in unipolar patients (Jernajczyk et al. 1993).

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Materials and methods

Ten healthy normal male volunteers [age 37±12 (mean±SD)] participated in this study. Each was evaluated with a full medical and psychiatric history, structured psychiatric diagnostic interview (SCID), physical examination, routine laboratory examinations, and one adaptation night of polygraphic sleep recording to rule out sleep apnea or nocturnal myoclonus. Following a baseline night of sleep recording, subjects had 3 nights in the sleep laboratory, separated by at least 48 h, on which they were administered either placebo or ipsapirone (10 and 20 mg by mouth) 15 min before bedtime in double-blind, randomized order. Sleep records were scored visually by Rechtschaffen and Kales (Rechtschaffen and Kales 1968) criteria by well trained technicians who were blind to drug conditions. LEM was measured by W.J. in seconds between the onset of each REM period and the appearance of the first rapid eye movement for that REM period, as previously described, and was averaged for the night to define M-LEM. Interrater reliability for scoring LEM was 0.81 (W.J.).

Tests for normality of continuous variables were made using the Shapiro-Wilk W and the Kolomogorov D statistics in conjunction with plots of the distribution of the data (Shapiro and Wilk 1965; Stephens 1974). No significant departure from normality was detected. Data were statistically analyzed by ANOVA with repeated measures using the BMDP statistical software.

Results

As predicted, ipsapirone significantly prolonged REM latency and REM latency corrected, and reduced REM% at both doses compared with placebo (Table 1 and Figs 1–4). In addition, it prolonged M-LEM at both doses, as well as LEM for the first REM period (LEM_1). The higher dose, 20 mg, reduced REM time and the REM density of the first REM period (REMP#1density) compared with placebo. In addition, the higher dose increased sleep latency and lowered sleep efficiency compared with placebo. Moreover, the higher dose, 20 mg, increased sleep latency and reduced total sleep time and sleep efficiency compared with the lower dose, 10 mg.

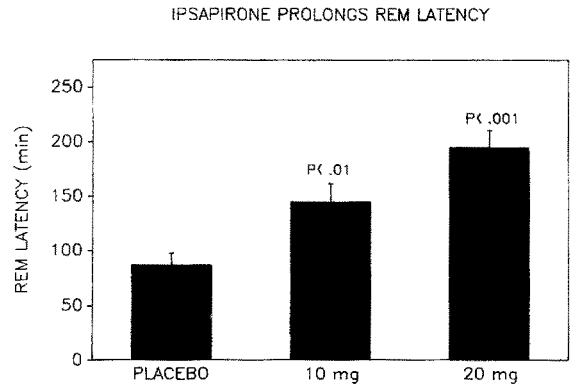

Fig. 1. Dose dependent prolongation of REM latency by ipsapirone in normal volunteers (n=10). Probability values over bars are pairwise contrast with placebo. ANOVA: P<0.001, F=14.84, df=2,18

No clinically significant side effects or behavioral changes were observed, although some nausea and fragmented sleep was observed at the 20 mg dose.

Discussion

These results with ipsapirone in humans provide further support for the hypothesis based on animal studies that $5HT1_A$ receptors can mediate serotonergic inhibition of REM sleep and its phasic events, such as the pontine geniculate occipital (PGO) electrical waves (McGinty et al. 1973; Shouse and Siegel 1992). Together with studies conducted by ourselves (Gillin et al. 1991) and others (Spiegel 1984) with cholinergic agonists and antagonists, this result is compatible with the reciprocal interaction hypothesis for the regulation of non-REM and REM sleep, namely, that cholinergic neurons facilitate REM sleep or components of it, while serotonergic (and possibly noradrenergic) mechanisms inhibit REM sleep (Hobson et al. 1975). Since this study did not systemati-

Table 1. Effect of ipsapirone on sleep in normal volunteers (n=10)

Sleep measure	Placebo	10 mg	20 mg	F
Sleep latency	16± 5	17± 6[i]	35±10[g]	3.55[a]
Total sleep time	407±12	416± 6[j]	382±14	5.59[b]
Sleep effciency	90.2± 2.3	92.3± 1.6[j]	84.9± 2.9[e]	9.22[c]
Stage 2	239± 6	268± 9	253±10	1.39
Delta (stages 3&4)	48±11	43± 8	41±13	0.28
REM sleep	97± 6	80± 7	63± 7[h]	9.94[c]
REM%	23.9± 1.1	19.3± 1.8[e]	16.1± 1.5[h]	9.79[c]
REM latency	87±11	145±17[g]	195±16[h]	14.84[d]
EM latency-A	85±11	141±17[g]	174±15[h]	13.36[d]
REM#1 duration	19± 3	15± 2	19± 5	0.29
REM density	19± 0.1	1.8± 0.2	1.7± 0.2	0.78
REMP#1 density	1.7± 0.1	1.4± 0.2	1.0± 0.3[f]	5.16[c]
M-LEM	28± 9	76±27[g]	80±46[h]	10.45[c]
LEM_1	23±18	71±46[d]	103±90[e]	4.89[b]
LEM_2	35±18	76±89	40±28	1.63

Mean±SEM. Values are in minutes except for percentage, REM density (0–8/min), and Latency to Eye Movements (LEM) (s)
ANOVA with repeated measures, df=2,18
[a]P< 0.05, [b]P< 0.025, [c]P< 0.01, [d]P< 0.001
Pairwise comparison with Placebo:
[e]P< 0.05, [f]P< 0.025, [g]P< 0.01, [h]P< 0.001
Pairwise comparison between ipsapirone 10 and 20 mg:
[i]P< 0.05, [j]P< 0.025

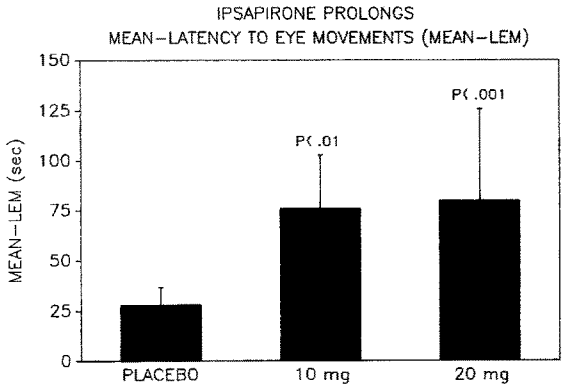

Fig. 2. Dose dependent prolongation of Mean Latency to Eye Movements (*M-LEM*) by ipsapirone. ANOVA: $P<0.01$, $F=10.45$, $df=2,18$

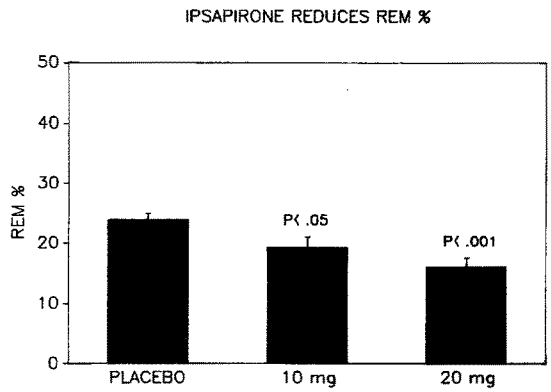

Fig. 4. Dose dependent inhibition of REM% by ipsapirone. ANOVA: $P<0.01$, $F=9.79$, $df=2,18$

cally investigate other serotonergic receptors, the present finding does not exclude the possibility that non-$5HT1_A$, serotonergic receptors also inhibit REM sleep.

While the present results in humans are consistent with preclinical studies indicating that serotonergic agonists, acting at the $5HT1_A$ receptor on cholinergic neurons, inhibit REM sleep, the current methodology does not address the neuroanatomic sites or precise pharmacological mechanisms of action of orally administered ipsapirone on sleep mechanisms. For example, ipsapirone is also known to directly reduce neuronal discharge in the dorsal raphe, possibly by stimulation of somatodendritic 5-HT1A receptors (Adrien et al. 1992). Furthermore, with the recent cloning of the 5-HT7 receptor, it has been suggested that some $5HT1_A$ receptor agonists are active on this newly discovered receptor and may influence circadian sleep-wake activity (Lovenberg et al. 1993). The 5-HT7 receptor may alter the phase position of the suprachiasmatic nucleus. Thus, ipsapirone is probably not pharmacologically specific at a single receptor subtype and may act at numerous neuroanatomic sites which regulate sleep-wake behaviors.

It is of interest that ipsapirone dramatically prolonged M-LEM and LEM_1, even at a lower dose than it affected REM density for the whole night and for the first REM period. The present results suggest that LEM may be a more sensitive indicator of the phasic events of REM sleep than REM density. We have previously reported that M-LEM was shorter in both bipolar and unipolar depressed patients than in normal controls, even though REM latency was normal in both studies (Jernajczyk 1986; Jernajczyk et al. 1993). Perhaps LEM can be used to assess central serotonergic activity in humans, including patients with depression or other neuropsychiatric disorders in whom serotonergic abnormalities have been postulated. Further research is needed to test this hypothesis. For example, short REM latency, short M-LEM, and elevated REM density, which are commonly reported in depression and other psychiatric disorders (Benca et al. 1992), may reflect an increased ratio of cholinergic to serotonergic/noradrenergic neurotransmission (Sitaram et al. 1976; Gillin et al. 1979; Gillin 1993).

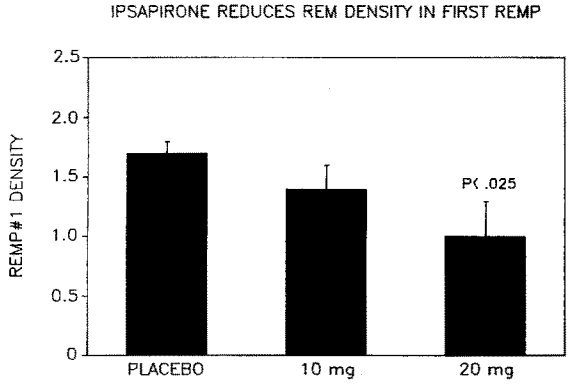

Fig. 3. Dose dependent inhibition of REM density by ipsapirone. ANOVA: $P<0.01$, $F=5.16$, $df=2,18$

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