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Ipsapirone, a 5-HT_{1A} Agonist, Suppresses REM Sleep Equally in Unmedicated Depressed Patients and Normal Controls

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To determine whether ipsapirone, a 5-HT_{1A} agonist, differentially suppresses REM sleep in depressed patients compared with normal controls, we administered placebo, ipsapirone 10 mg, or ipsapirone 20 mg in a double-blind, random order before bedtime in 18 unmedicated patients with depression and 16 age-matched, gender-matched normal controls. Compared to placebo, ipsapirone affected REM sleep measures equally in depressed patients and controls as follows: (1) increased REM latency; (2) reduced total REM percent, REM time, and REM density; and (3) delayed the onset of REM sleep. In addition, ipsapirone had similar effects in patients and controls in other sleep measures: (1) reduced total sleep time; (2) delayed sleep onset time; and (3) increased sleep latency, stage 1%, stage 2%, the amount of stage 3 & 4 sleep in the first non-REM period, and wake time after sleep onset. The study does not support the hypothesis that downregulated 5-HT_{1A} receptors mediate the pathophysiology or sleep disturbances of depression, although further studies are needed as these patients did not differ from controls in baseline sleep measures. **[Neuropsychopharmacology 15:109–115, 1996]**

KEY WORDS: *Serotonin; Mood disorder; REM latency*

Diminished functional serotonergic neurotransmission at the 5-HT_{1A} receptor may be involved in the pathophysiology of depression and the mechanisms of antidepressant pharmacotherapy. Some of the data for and against this hypothesis includes:

1. Direct measures of 5-HT_{1A} receptors in autopsied brain: although Cheetham et al. (1990) reported reduced 5-HT_{1A} receptor activity in drug-free suicides compared with controls, this finding was not supported by Arranz et al. (1994).
2. A "blunted" hypothermic response to 5-HT_{1A} agonists in depression compared with normal controls (Lesch et al. 1990b; Cowen et al. 1994).
3. Decreased adrencorticotrophic hormone (ACTH) and cortisol release. This finding was reported by Lesch et al. (1990a) following ipsapirone administration, associated with increased basal cortisol secretion, but abnormal cortisol secretion was not supported following buspirone administration (Meltzer and Maes 1994).
4. Decreased release of prolactin following buspirone administration was reported by Moeller et al. (1994) but not by Meltzer and Maes (1994). A similar decrease following chlomipramine administration was found by Anderson et al. (1992).
5. Antidepressant benefits during treatment with the 5-HT_{1A} agonists flesinoxan (Grof et al. 1993) and buspirone (Robinson et al. 1990).
6. Downregulation of 5-HT_{1A} receptors during antide-

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pressant treatment (Stahl 1992; Rausch et al. 1990). In addition, Curtis et al. (1993) have reported that genetic linkage analysis of five Icelandic pedigrees excluded the 5-HT_{1A} receptor in bipolar disorder.

A "downregulated" 5-HT_{1A} receptor may also be involved in the polygraphic sleep abnormalities associated with depression and some other psychiatric disorders, such as short REM latency (the elapsed time between the onset of sleep and the first REM period), reduced stages 3 and 4 (delta) sleep, and increased REM time and REM density (a measure of ocular activity during REM sleep) (Benca et al. 1992). Recent advances have suggested that normal REM sleep is promoted by cholinergic neurotransmission and inhibited by noradrenergic and serotonergic mechanisms. To briefly recapitulate, REM sleep—or at least its phasic events (eye movements and pontine geniculate occipital (PGO) spikes)—is promoted by cholinergic neurons originating within the peribrachial region, including the lateral dorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei (Shiromani et al. 1988). The cholinergic neurons in the LDT/PPT are inhibited by noradrenergic and serotonergic neurons in the locus coeruleus and dorsal raphe, respectively (Steriade and McCarley 1990; Siegel 1989; Jones 1991). An inhibitory, monosynaptic 5-HT_{1A} receptor apparently mediates serotonergic modulation over the LDT/PPT (Luebke et al. 1992). In addition to promoting REM sleep, cholinergic mechanisms inhibit stages 3 and 4 (delta) sleep through both cholinergic terminals from the basal forebrain to the cortex (Buzsaki et al. 1988) and from the LDT/PPT to the thalamus (Steriade and McCarley 1990; Steriade et al. 1991). Thus, decreased functional serotonergic neurotransmission from the dorsal raphe might disinhibit LDT/PPT neurons, resulting in a shortened REM latency, increased REM density, and decreased delta sleep.

Consistent with these concepts, the 5-HT_{1A} agonist 8-OH-DPAT inhibits REM sleep whether administered directly into the LDT in cat (Sanford et al. 1994) or systematically (Dugovic et al. 1989). Similarly, REM inhibition is also reported following systemic administration of other 5-HT_{1A} agonists (Depoortere 1988), such as eltoprazine (Quattrochi et al. 1993), m-chlorophylpiperazine (m-CPP) (Sanford et al. 1994), or buspirone (Lerman et al. 1986) in animals, or m-CPP (Lawlor et al. 1991) and buspirone (Seidel et al. 1985) in humans. We earlier reported that ipsapirone had similar REM-sleep-suppressing effects in normal humans (Gillin et al. 1994). Furthermore, administration of the tryptophan-free amino acid drink (TFD), which presumably depletes the brain of tryptophan and serotonin, shortens REM latency and increases REM percent in normal volunteers (Bhatti et al. 1995).

The purpose of this study was to determine whether depressed patients would show less inhibition of REM sleep than normal controls following administration of ipsapirone at bedtime. Based on the hypothesis that the 5-HT_{1A} receptor is downregulated in depression, we predicted that ipsapirone would prolong REM latency and reduce REM percent to a lesser extent in depressed patients than in normal controls.

METHODS

Thirty-four subjects completed the study: 18 patients with depression (9 men, 9 women, age = 40.2 ± 9.3 years) and normal controls (10 men, 6 women, age = 41.7 ± 9.5 years). All subjects were recruited from a pool of depressed patients seeking admission to the San Diego VA Medical Center, as well as those who responded to public announcements and advertisements for patients with depression and normal controls. Recruitment was coordinated by the Recruitment Core of the University of California-San Diego (UCSD) Mental Health Clinical Research Center (MHCRC). Both patients and normal controls were evaluated by the UCSD MHCRC Diagnostic Core with a full medical and psychiatric history, physical examination, routine screening laboratory tests (CBC, urinalysis, laboratory tests, EKG, HIV screen); a structured psychiatric interview (SCID based on DM-III-R criteria); and ratings for depression (Hamilton Rating Scale of Depression [HRSD] 17- and 24-item versions). Following the diagnostic evaluation, the final diagnosis was arrived at by the weekly Consensus Conference (chaired by JK and MR); interviewer reliability is tested twice a year. All patients and normal subjects were physically healthy at the time of the study. Ten of the 16 controls were included in our preliminary publication on the effects of ipsapirone on sleep. Six of the 18 patients were inpatients at the time of the study.

Seventeen patients met diagnostic criteria for major depressive disorder (11 recurrent, 6 single episode) and one patient for bipolar depression. Three patients met diagnostic criteria for melancholia, one for psychotic features, 11 for moderate, and 5 for severe depression; none met criteria for seasonal affective disorder. Secondary diagnoses included alcohol abuse or dependence in full remission (n = 6), cocaine or amphetamine abuse or dependence in full remission (n = 5), cannabis dependence in full remission (n = 4), opioid abuse in full remission (n = 1), panic disorder (n = 1), panic disorder in full remission (n = 1), simple phobia (n = 1), social phobia (n = 5), social phobia in full remission (n = 1), and posttraumatic stress disorder (n = 2). Six of the patients had only one diagnosis, seven had two Axis I diagnoses, four had three diagnoses, and one had four diagnoses. Depression was the primary reason for seeking treatment prior to enrollment in the research protocol. Of the active comorbid diagnoses, 1 patient had

panic disorder, 1 patient had simple phobia, 5 patients had social phobia, and 2 patients had posttraumatic stress disorder.

None of the normal controls met diagnostic criteria for a past or present psychiatric disorder. None of the subjects had been treated with any psychoactive or sleeping medication within 2 weeks of the onset of the study.

All subjects were screened during the first night of two nights in the sleeping laboratory with all-night pulse oximetry and tibial EMG, in addition to routine recordings of EEG, EOG, submental EMG, and EKG to rule out sleep disorders. The second night in the laboratory was a baseline night. The main data for this study were collected on three experimental nights: placebo, ipsapirone 10 mg, or ipsapirone 20 mg PO administered in a double-blind, random order at lights-out approximately 11:00 P.M. (2300 military time). At least 48 hours passed between each experimental night. Sleep records were scored visually according to Rechtschaffen and Kales criteria (1968) by well-trained technicians who were blind to treatment condition. Subjects also filled out a 20-item side effect symptom checklist each morning after dressing; each item was scored on a 0 to 4 scale.

Data were examined for homogeneity of variance and normal distribution prior to statistical analysis by a two-way repeated-measures analysis of variance (ANOVA): groups (patients versus controls) and dose (placebo, ipsapirone 10 mg, and ipsapirone 20 mg). Because previous studies reached conflicting conclusions on whether or not the 5-HT_{1A} receptor is downregulated in depression, we required a p value $< .05$ (two-tailed) for statistical significance.

RESULTS

The HRSD was obtained weekly and did not change over the course of the sleep study. The results of the 17-item HRSD scale during the experimental period were 19.2 ± 0.9 (mean ± SEM; range = 14, from 12 to 26) for patients and 0.1 ± 0.1 (range = 1, from 0 to 1) for controls; for the 24-item scale they were 25.8 ± 1.2 (range = 17, from 16 to 33) for patients and 0.1 ± 0.1 (range = 1, from 0 to 1) for controls. The two groups did not differ

Table 1. Dose-Dependent Effects of Ipsapirone on Polygraphic Sleep Measures in Depressed Patients and Normal Controls[a]

	Patients (n = 18)			Controls (n = 16)			Drug Dose
Sleep Measure	**Placebo**	**10 mg**	**20 mg**	**Placebo**	**10 mg**	**20 mg**	$F_{2,64}$
Sleep onset	23:22: ± :07	23:25 ± :07	23:35 ± :08[e]	23:16 ± :04	23:12 ± :05	23:26 ± :09	3.32[a]
Sleep latency	19 ± 3	22 ± 4	32 ± 6	20 ± 14	14 ± 4	31 ± 8	8.13[d]
Total sleep	405 ± 5	382 ± 8[f]	381 ± 11	398 ± 8	389 ± 9	370 ± 11[g]	8.33[d]
Stage 1%	6.3 ± 0.7	6.9 ± 0.7	7.6 ± 0.9	5.9 ± 0.9	6.7 ± 0.9[e]	7.2 ± 0.7	4.57[b]
Stage 2%	58.2 ± 2.4	60.3 ± 2.4	63.9 ± 3.1[b]	57.1 ± 1.7	64.1 ± 1.9[g]	64.0 ± 2.0[g]	13.29[d]
Stage 3%	6.9 ± 1.0	8.9 ± 1.4	6.8 ± 1.3	7.9 ± 0.9	7.8 ± 1.1	9.9 ± 1.0	1.25
Stage 4%	3.9 ± 1.4	4.4 ± 1.4	5.1 ± 1.8	4.8 ± 1.5	3.1 ± 1.4	3.7 ± 1.5	0.36
Delta %	10.8 ± 2.2	13.3 ± 2.4	11.9 ± 2.8	12.7 ± 2.1	10.9 ± 2.1	13.6 ± 2.0	0.39
REM latency corrected	74 ± 10	137 ± 10[h]	180 ± 15[h]	68 ± 6	144 ± 15[h]	190 ± 11[h]	62.94[d]
REM onset	00:39 ± :09	01:55 ± :08[h]	02:55 ± :15[h]	00:25 ± :08	01:54 ± :15[h]	03:07 ± :11[h]	76.65[d]
REM %	24.7 ± 1.3	19.5 ± 1.1[h]	16.6 ± 1.1[h]	24.3 ± 1.0	18.4 ± 1.3[h]	14.8 ± 1.2[h]	48.54[d]
REM density	1.9 ± 0.1	1.7 ± 0.1	1.6 ± 0.1[e]	2.0 ± 0.2	1.7 ± 0.2[f]	1.7 ± 0.2[e]	6.69[c]
REM #1	24 ± 4	23 ± 2	24 ± 4	18 ± 2	21 ± 3	17 ± 2	0.11
NREM #1 Delta	21 ± 4	42 ± 8[h]	38 ± 9[g]	25 ± 5	36 ± 6	44 ± 7[f]	12.22[d]
WASO	21 ± 3	33 ± 5[e]	32 ± 4	28 ± 3	40 ± 5	43 ± 5[e]	4.40[b]

Means ± SEM. Sleep measures are in minutes except for REM density (a measure of ocular activity during REM sleep, scored on a scale of 0 to 8 minutes of REM sleep) and percentages of total sleep time. Clock time is in military time. REM latency corrected is the time from onset of sleep to onset of first REM period, minus intervening awake time. REM #1 duration is the duration of the first REM period. WASO is the wake time after sleep onset. F values measure the effect of dose of drug with the following p values.

[a] $p < .05$.
[b] $p < .025$.
[c] $p < .01$.
[d] $p < .001$.

Pairwise comparison with placebo following a significant ANOVA measured with the following p values.

[e] $p < .05$.
[f] $p < .025$.
[g] $p < .01$.
[h] $p < .001$.

Drug-Dose refers to dose-dependent within-subjects ANOVA.

on any polygraphic sleep measure at either baseline (data not shown) or after receiving placebo (Table 1).

Ipsapirone, as predicted, significantly inhibited REM sleep in a dose-dependent fashion in both patients and controls compared with placebo. Contrary to our a priori hypothesis, however, no significant group-by-dose interaction was found. As shown in Table 1, the drug significantly prolonged REM latency corrected (the elapsed time between the onset of sleep and the first REM period, minus any awake time), delayed REM onset time, reduced REM percent, and reduced REM density (for both the whole night and the first REM period). Ipsapirone also significantly reduced REM time and prolonged REM latency but did not significantly affect the duration of the first REM period (not shown for reasons of space).

In addition, ipsapirone caused a significant but mild delay of sleep onset time (SOT), prolonged sleep latency, reduced total sleep time, and increased stage 1%, stage 2%, and wake time after sleep onset (WASO). The total amount of time (in minutes) spent in stages 1, 2, 3, or 4 was not significantly affected, although the amount of time spent in stages 3 and 4 sleep during the first non-REM period was significantly increased, consistent with the prolongation of REM latency.

Post hoc examination of the non-REM sleep data showed significant interaction effects for stage 2 (minutes), ($p < .05$, $F_{2,64} = 3.35$), stage 3 (minutes/night), ($p < .05$, $F_{2,64} = 3.63$), and stage 3% ($p < .02$, $F_{2,64} = 4.84$). Compared with placebo, stage 2 values were higher in controls at both doses and in patients at 20 mg, but lower in patients at 10 mg. Both stage 3 and stage 3% values were increased in patients at 10 mg and in controls at 20 mg, whereas both sleep measures tended to decrease at 20 mg in patients and 10 mg in controls.

If the subjects had any symptoms during the night, these were recorded by the sleep technicians. Both patients and controls reported more symptoms to the sleep technician during the night following 20 mg than with either placebo or 10 mg. For controls, 8 of 16 subjects reported symptoms at 20 mg, but only 2 did so with placebo or 10 mg. For patients, 12 of 18 reported symptoms after 20 mg but only 7 did so after placebo or 10 mg. Symptoms at night were mostly GI discomfort, such as relatively mild nausea. The symptoms were apparently short-lasting since, as shown in Table 2, the total score for side effect symptoms noted by the subjects on awakening in the morning did not significantly increase with either dose of ipsapirone compared with placebo. Patients did have higher scores of side effect symptoms than controls on all three mornings.

Table 2. Total Number of Side Effects on the Morning Following Placebo or Ipsapirone Administration

	Placebo	10 mg	20 mg
Controls	2.0 ± 2.7	2.2 ± 2.5	2.1 ± 2.2
Patients	8.3 ± 6.0	8.8 ± 5.9	10.3 ± 6.8

We also calculated absolute change scores for various sleep measures (baseline versus placebo, ipsapirone 10 mg, and ipsapirone 20 mg) for patients and controls. Changes induced by the ipsapirone in REM latency and REM latency corrected, REM time, sleep latency, and sleep efficiency were almost identical in both patients and controls and did not differ statistically.

We tested the hypothesis that baseline measures of REM latency corrected were related to the magnitude of the change in REM latency induced by the two doses of ipsapirone. We correlated baseline REM latency corrected with the magnitude of the change induced by ipsapirone 10 mg and 20 mg compared with placebo (REM latency corrected on the ipsapirone dose minus the value on placebo). Because the rank-order correlations were close to zero for both doses, this hypothesis was not supported.

DISCUSSION

These results did not confirm our a priori hypothesis that ipsapirone would exert a "blunted" inhibition of REM sleep in depressed patients compared with normal controls. Consistent with our hypothesis and our earlier publication, however, it did prolong REM latency, delay the time of night at which REM sleep first occurred, and reduce REM percent and REM density in patients and controls more or less equally. In addition, it delayed the onset of sleep and reduced sleep time. Interestingly, when the duration of the first non-REM period (that is, REM latency) was increased, the total amount of time spent in stages 3 and 4 sleep during the first non-REM period also increased.

The failure to find ipsapirone-induced differences in REM sleep measures between patients and normal control groups may be related to the similarity in sleep measures at baseline and placebo conditions in the patients compared with the normal controls. Even though the patients met formal diagnostic criteria for depression and were rated as at least moderately depressed according to the HRSD, these observations suggest no abnormality in the 5-HT_{1A} receptors within neural circuits thought to be responsible for shortening REM latency in these patients. In addition, because the magnitude of the effect of ipsapirone-induced suppression of REM sleep was not correlated with baseline REM latency, the results suggest that baseline REM latency is not related to the 5-HT_{1A} receptor sensitive to ipsapirone.

The mechanisms by which ipsapirone and other

5-HT_{1A} agonists exert their pharmacological effects on the brain following systemic administration remain incompletely understood. At least three possibilities are relevant to the current study: (1) Ipsapirone directly inhibits a postsynaptic 5-HT_{1A} on cholinergic neurons in the LDT/PPT, in accord with the work of Luebke et al. (1992); (2) ipsapirone directly inhibits firing of serotonergic neurons via serotonergic somatodendritic 5-HT_{1A} autoreceptors on DRN neurons, as shown, for example, by Fornal et al. (1994); and (3) ipsapirone affects not only 5-HT_{1A} receptors but also 5-HT_7 receptors, which have recently been described within the suprachiasmatic nucleus (SCN), which is probably the circadian pacemaker (Lovenberg et al. 1993). Other possible sites and modes of pharmacological action are also possible. Of the three possibilities discussed, we favor the first in the interpretation of the inhibitory effects of ipsapirone on REM sleep. The current observation is consistent with considerable other data suggesting that serotonergic mechanisms inhibit REM sleep, including not only the previously cited study of Luebke et al. (1992) but also the virtual cessation of firing within the DRN shortly before and during REM sleep (McGinty and Harper 1976). The second possibility—that ipsapirone inhibits single-cell firing within the DRN—presents a potential challenge to the current hypothesis that serotonergic neurons inhibit REM sleep: If it shuts down firing in the DRN, why is REM sleep inhibited rather than enhanced following systemic administration ipsapirone? At least two possible interpretations come to mind. First, systematically administered ipsapirone presumably directly inhibits LDT/PPT neurons, in addition to inhibiting DRN firing. Second, Fornal et al. (1994) have suggested that 5-HT_{1A} agonists and antagonists exert less effect on firing rates in DRN neurons during behavioral quiescence (including sleep) than during behavioral activation. To our knowledge, no one has studied DRN firing rates during non-REM and REM sleep following the administration of ipsapirone or other 5-HT_{1A} agonists. Finally, regarding the third possibility discussed, ipsapirone significantly delayed the onset of the first REM period. Whether or not ipsapirone might have inhibited REM sleep by an effect on the circadian pacemaker seems unlikely but cannot be entirely rejected without further data.

Other groups also found no consistent difference between depressed patients and normal controls in the effects of serotonergic challenges on sleep measures. Ritanserin, a 5-$HT_{2A/C}$ antagonist, was reported by Da Roza Davis et al. (1992a; 1992b) to increase stages 3 and 4 sleep normally in patients with either generalized panic disorder or remitted depression in depressed patients compared to controls, but not by Staner et al. (1992). In addition, another 5-$HT_{2A/C}$ antagonist, cyproheptadine, was reported by Sharpley et al. (1990) to increase slow-wave sleep in the normal controls but not in depressed patients maintained on tricyclic antidepressants; it reduced REM sleep in both normal controls. Furthermore, Williams et al. (1994) reported that metachorphenylpiperazine (mCPP), which apparently possesses both 5-HT_{2C} agonist and 5-HT_{2A} antagonist properties, suppressed slow-wave sleep equally in depressed patients and controls.

In contrast, both cholinergic and noradrenergic pharmacological challenges, using REM sleep as an outcome measure, have differentiated patients with depression and normal controls. For example, depressed patients have shown significantly more rapid induction of REM sleep following administration of arecoline (Sitaram et al. 1980) and RS 86 (Berger et al. 1989; Riemann et al. 1994) and more awakening following administration of physostigmine shortly after sleep onset (Berger et al. 1983). Schreiber et al. (1992) have suggested that a rapid induction of REM sleep with RS 86 may identify who is at high risk for mood disorders. Schittecatte et al. (1992) reported that intravenous administration of clonidine, a noradrenergic $alpha_2$ agonist during the second non-REM period delayed the onset of REM sleep to a lesser degree in depressed patients than in normal controls.

In summary, except for post hoc effects on stages 2 and 3 sleep, ipsapirone had similar effects on sleep in both depressed patients and normal controls. The weight of the current available evidence does not support a differential effect of serotonergic challenges (ipsapirone, ritanserin, cyproheptadine, or mCPP) on sleep in depressed patients compared with controls. In contrast, the effects of cholinergic agonists (arecoline, RS 86, and physostigmine) and of the $alpha_2$ agonist clonidine appear to differentiate depressed patients from controls. The relative role of cholinergic, noradrenergic, and serotonergic mechanisms in the pathophysiology of depression and its sleep manifestations deserves further investigation.

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