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Age-Related Effects of Scopolamine on REM Sleep Regulation in Normal Control Subjects: Relationship to Sleep Abnormalities in Depression

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In order to assess the influence of development on the regulation of rapid eye movement (REM) sleep by cholinergic systems, the REM sleep responses to scopolamine were assessed in five normal adolescent and seven adult control subjects in this preliminary investigation. Subjects were studied on two separate occasions for three consecutive nights. Subjects received placebo or scopolamine (1.5 ug/kg, i.m.) on night 2; night 3 was considered the "recovery" night. As expected, scopolamine delayed REM latency and suppressed REM sleep on night 2 in both the adolescents and adults. Subtle developmental differences occurred, with scopolamine having a tendency to suppress REM sleep less effectively in younger subjects. On night 3, REM latency was shortened and REM sleep was increased to comparable extent in both the adolescents and adults. The comparable REM sleep responses to scopolamine between normal adolescents and adults, particularly on night 3, are discussed in relation to the age-related expression of REM sleep abnormalities in depression. ***[Neuropsychopharmacology 21:723–730, 1999]*** *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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Electroencephalographic (EEG) sleep changes associated with major depressive disorder are among the most well replicated findings in adult patients (for a review, see Benca et al. 1992). Perhaps the most dramatic changes occur with respect to rapid eye movement (REM) sleep measures.

Despite the evidence for continuities in mood disorders across the life span (Kovacs 1996), the manifestation of comparable REM sleep abnormalities appears to occur less frequently in early onset depression (reviewed in Rao et al. 1996). The mechanisms for this disparity are unclear. One possibility is that circadian and ultradian rhythms are more desynchronized in youngsters with depression, thus not allowing the REM sleep abnormalities, particularly the shortening of REM latency, to be easily detected (Teicher et al. 1993). Another possibility is that slow-wave sleep pressure is greater than REM sleep pressure in youngsters so that the shortening of REM sleep latency is constrained (Borbely 1982).

Furthermore, it is possible that the neurotransmitter circuitry involved in REM sleep regulation is not fully mature in youngsters. Thus, shortened REM latency or increased REM activity and density in depression

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might not be able to occur. Animal studies suggest that the cortical cholinergic projections may be the last developing components of the reticular core (Coyle and Yamamura 1976). We previously found that the delay in REM latency in response to scopolamine, a non-specific muscarinic cholinergic antagonist, occurs to comparable degrees in both normal adolescents and adults suggesting that muscarinic cholinergic tone is working in both age groups (McCracken et al. 1997; Poland et al. 1997). Similarly, the REM sleep response to scopolamine, particularly REM latency, also is relatively intact in adult and adolescent patients with depression (McCracken et al. 1997; Poland et al. 1997).

In contrast to scopolamine, adults with major depression show an enhanced shortening of REM latency in response to cholinergic agonists, and one study indicates that this abnormal response also is observed in prepubertal children (Dahl et al. 1994). However, it still remains unclear as to why the majority of studies in depressed youngsters have not shown the typical REM sleep abnormalities, particularly shortened REM latency, which are observed in adult depressed patients.

Developmental differences in REM sleep manifestations associated with depression may have implications for the treatment of depression in youngsters. Compared to adults, children and adolescents suffering from depression appear to respond less robustly to traditional antidepressant treatments (for a review, see Birmaher et al. 1996). At least in adults, one feature common to many antidepressants is the ability to suppress REM sleep and prolong REM latency (Sharpley and Cowen 1995; Staner et al. 1995; Vogel et al. 1990). Some investigators have suggested that baseline REM sleep characteristics, as well as the extent of REM sleep suppression on acute antidepressant treatment are predictive of subsequent antidepressant efficacy (Gillin et al. 1978; Höchli et al. 1986; Kupfer et al. 1994; Rush et al. 1989; Sharpley and Cowen 1995; Thase et al. 1997; Vogel et al. 1990). Even in children and adolescents, there is preliminary evidence that baseline reduced REM latency and REM sleep suppression on administration of antidepressants may be predictive of antidepressant treatment response (Emslie and Kowatch 1996; Kupfer et al. 1979). However, baseline reduced REM latency and REM sleep suppression with antidepressant treatment may be less prevalent in juvenile populations (Armitage et al. 1997; Benca et al. 1992; Knowles and MacLean 1990; Rao et al. 1996).

In addition to REM sleep suppression on acute antidepressant administration, other adaptive changes occur in adults. For example, withdrawal from antidepressants and cholinergic antagonists results in temporary increase in REM sleep (Gillin et al. 1991a; Sagalés et al. 1975; Salin-Pascual et al. 1993; Sharpley and Cowen 1995; Staner et al. 1995; Vogel et al. 1990). To our knowledge, there are no studies on the withdrawal effects of antidepressants or anticholinergics on REM sleep in children or adolescents. One study noted that discontinuation of clomipramine in young rats after a two-week treatment during the neonatal period was not accompanied by "rebound" increase in REM sleep (Mirmiran et al. 1981). Although data from animals may not be applicable to humans, this observation, together with other EEG sleep findings in children and teenagers, suggests that there may be developmental differences in REM sleep regulation.

In order to study this issue further, in this pilot study, sleep patterns in normal adolescents and adults were studied following the administration of scopolamine and on the recovery night. Of particular interest was whether adolescents demonstrate acute shortening of the REM latency and other REM rebound effects on the recovery night to the same degree as adults.

MATERIALS AND METHOD

Participants

A total of 12 subjects between the ages of 14 and 42, five adolescents (ages: 14–18) and seven adults were studied. All participants were evaluated for psychopathology with the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al. 1986). Also, psychopathology in the first-degree relatives was assessed, using the subject or parent (in the case of adolescents) as an informant. In addition to the SCID interview, the clinician rated the severity of depressive symptoms using the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960).

The subjects had no personal history of a major psychiatric disorder or history of a major psychiatric disorder in any known first-degree relative. All participants had HAM-D scores < 2. Subjects were medically healthy, as determined by physical examination, electrocardiogram, full chemistry panel, thyroid function tests, and urine drug screens. All participants were free from medication use for at least two weeks. In order to rule out known sleep disorders, a sleep questionnaire was filled-out and a sleep log was maintained for at least one week prior to the study. Subjects with a personal history of a major sleep disorder or a family history of narcolepsy were excluded from the study. Participants were screened also for the presence of sleep disorder(s) on the first night of the sleep protocol.

Sleep Protocol and Scoring of Sleep Records

Subjects were studied twice for three consecutive nights, approximately one week apart. On all nights, conventional EEG electrodes were attached by 8:00 PM, and sleep recordings were made from 11:00 PM (lights out) to 7:00 AM. On night 2 of each three-night session, subjects were administered either saline or scopolamine

(1.5 μg/kg,i.m.) at 11:00 PM in a double-blind, randomized fashion. Night 3 was considered the recovery night.

Sleep records were coded and scored blindly according to standard criteria (Rechtschaffen and Kales 1968). REM latency was calculated using lenient and strict definitions. For the lenient definition, REM latency was defined as the time between sleep onset (the first minute of any stage of sleep) and the first 30 seconds of REM sleep. The strict definition was defined as the time between sleep onset (first minute of stage 2 or deeper sleep, followed by at least 9 minutes of stage 2 or deeper sleep, interrupted by no more than 1 minute of waking or stage 1) and the first REM period 3 minutes in length. Other REM measures, including REM activity and REM density, and additional sleep variables were scored according to the criteria of Kupfer (1976), as was done previously (Poland et al. 1989, 1997).

Statistical Analysis

Statistical analyses were performed utilizing two-way analysis of variance (ANOVA) with repeated measures, with adolescent versus adult as the between-subjects factor, whereas drug (placebo versus scopolamine) and night (treatment versus recovery) were the within-subject factors.

Due to modest sample sizes, analyses were restricted to the REM sleep measures based on a priori hypotheses. Where significant main and/or interaction effects for group, drug or night were observed, separate analyses were performed, using unpaired and paired *t*-tests, to locate significant differences. Alpha was set at 0.05. Pearson product-moment correlation coefficients were calculated to examine the relationship between age and change in REM sleep measures on treatment and recovery nights (delta REM sleep measures). Transformations were performed when data were not normally distributed. Only EEG data from the second and third nights of each three-night session were used in the statistical analyses, the first night being considered as an adaptation night.

RESULTS

REM Sleep Responses to Scopolamine in Adolescents versus Adults

Variables for the first REM episode on placebo and scopolamine nights as well as the recovery nights, in both adolescents and adults, are presented in Table 1. Baseline REM sleep measures were comparable between adolescents and adults. REM latency was effected by scopolamine. With the exception of REM duration, there was a main effect of the night on REM sleep measures. Furthermore, there was a significant drug × night interaction for REM latency and REM density. Compared to the placebo night, scopolamine prolonged REM latency, whereas it diminished REM activity and REM density in the adults. A similar trend was noted for all three measures in the adolescents, but they did not approach significance level. There was a significant re-

Table 1. REM Sleep Variables for First REM Episode (Mean ± SD) Following Placebo and Scopolamine (1.5 μg/kg, i.m.)

	Placebo		Scopolamine		Repeated Measures ANOVA					
	Treatment Night	Recovery Night	Treatment Night	Recovery Night	Drug	Night	Drug × Night	Drug × Group	Night × Group	Drug × Night × Group
REM latency (min)										
Adolescents	88.7 ± 23.7	96.7 ± 47.5	157.9 ± 62.1	71.1 ± 13.2[b]						
Adults	77.7 ± 12.4	81.6 ± 23.5	193.7 ± 88.7[a]	66.8 ± 20.5[b]	8.69*	16.44**	17.86**	1.37	0.79	0.52
REM activity (units)										
Adolescents	36.2 ± 27.5	39.4 ± 51.3	4.5 ± 2.7	38.3 ± 24.0[b]						
Adults	53.7 ± 38.3	62.3 ± 72.9	17.6 ± 9.8[a]	84.7 ± 66.8[b]	0.42	18.87***	3.56	0.07	2.22	0.35
REM density (units/min)										
Adolescents	2.3 ± 1.2	1.7 ± 1.4	0.8 ± 0.4	2.6 ± 1.4[a,b]						
Adults	2.2 ± 0.8	2.4 ± 1.4	1.2 ± 0.9[a]	3.3 ± 1.7[b]	0.30	19.68***	17.99**	0.15	1.87	0.32
REM duration (min)										
Adolescents	13.4 ± 6.4	15.9 ± 11.9	9.0 ± 6.7	13.9 ± 5.7						
Adults	23.9 ± 11.0	21.8 ± 14.4	17.6 ± 10.3	23.3 ± 12.2	0.44	1.76	0.76	0.01	0.20	0.21

* = $p \leq .05$; ** = $p \leq .005$; *** = $p \leq .001$.

[a] $p \leq .05$, placebo versus scopolamine, same night; [b] $p \leq .05$, treatment versus recovery night, scopolamine.

Table 2. REM Sleep Variables for the Entire Night (Mean ± SD) Following Placebo and Scopolamine (1.5 μg/kg, i.m.)

	Placebo		Scopolamine		Repeated Measures ANOVA					
	Treatment Night	Recovery Night	Treatment Night	Recovery Night	Drug	Night	Drug × Night	Drug × Group	Night × Group	Drug × Night × Group
REM activity (units)										
Adolescents	282.9 ± 97.9	262.4 ± 86.6	143.0 ± 69.0[a]	414.2 ± 163.9[a,b]						
Adults	238.3 ± 116.9	290.9 ± 103.7	102.3 ± 65.6[a]	402.6 ± 171.1[b]	0.02	54.92****	28.74****	0.19	1.57	0.19
REM density (units/min)										
Adolescents	3.1 ± 0.8	2.8 ± 0.7	2.1 ± 0.5[a]	3.6 ± 1.1[a,b]						
Adults	2.4 ± 0.9	3.0 ± 0.9	1.9 ± 1.1	2.9 ± 1.4	0.61	19.61***	6.97*	0.18	0.31	3.27
REM duration (min)										
Adolescents	90.8 ± 19.4	92.4 ± 14.8	72.5 ± 20.4[a,c]	111.7 ± 18.6[a,b]						
Adults	96.6 ± 25.1	96.7 ± 15.4	55.1 ± 16.7[a]	122.7 ± 22.7[a,b]	0.87	29.26****	51.05****	1.13	1.79	4.10
No. of REM episodes										
Adolescents	3.8 ± 0.4	3.8 ± 0.5	3.6 ± 0.6[c]	4.8 ± 0.5[a,b]						
Adults	4.3 ± 1.0	3.9 ± 0.9	2.9 ± 0.9[a]	4.6 ± 0.8[a,b]	0.05	14.74**	42.57****	15.82***	0.02	3.39
REM sleep (%)										
Adolescents	22.4 ± 4.8	21.8 ± 4.2	15.5 ± 3.4[a]	26.1 ± 4.2[a,b]						
Adults	24.1 ± 5.5	25.2 ± 3.5	14.2 ± 4.1[a]	31.4 ± 5.0[b]	2.49	59.63****	72.50****	0.07	4.97*	2.36

* = $p \leq .05$; ** = $p \leq .005$; *** = $p \leq .001$; **** = $p \leq .0001$.

[a] $p \leq .05$, placebo versus scopolamine, same night; [b] $p \leq .05$, treatment versus recovery night, scopolamine; [c] $p \leq .05$, adolescent versus adult, same night.

bound effect for all three measures on the recovery night following scopolamine treatment. The rebound effect was comparable between adolescents and adults. Among adolescents, the rebound effect in REM density was significantly greater than the placebo recovery night.

Table 2 shows REM sleep measures for the entire night during placebo and scopolamine treatments, as well as recovery nights, in both adolescents and adults. Baseline REM sleep measures were comparable between the two groups. There was a main effect of the night and drug × night interaction for each of the REM sleep measures. Again, scopolamine suppressed all aspects of REM sleep over the course of the night. Although no significant drug × night × group interactions occurred, some trends were present. With the exception of REM density and REM episode variables, the extent of REM sleep suppression was comparable between adolescents and adults. Reduction in REM density in the adults did not reach significance. Adolescents did not demonstrate reduction in REM episodes. On the scopolamine night, adolescents showed longer REM duration and more REM episodes compared to the adults. There was a significant rebound effect for all REM sleep measures on the recovery night following scopolamine treatment. Overall, the two groups did not differ significantly on the degree of rebound effect. In comparison with the placebo rebound effects, adolescents showed a trend for an even greater increase in all the REM sleep variables. In the adults, only REM duration and REM episodes were greater than the effects observed on the placebo rebound night.

Relationship between Age and REM Sleep Responses to Scopolamine

Pearson correlation coefficients between age and delta REM sleep variables on the treatment night revealed marked variability (see Table 3). Only total REM duration showed a significant correlation with age. In summary, younger subjects showed less REM sleep suppression with scopolamine treatment, specifically in the tonic REM sleep measures. Phasic REM sleep measures (namely, delta REM activity and delta REM density) showed weak relationships with age. In examining the association between age and delta REM sleep measures on the recovery night, none of the variables were significantly influenced by age. The correlation coefficients were of small magnitude (range −0.22 to +0.18). Delta REM latency on the recovery night plotted against age is depicted in Figure 1 ($r = 0.18$, $df = 11$, NS).

Table 3. Relationship between Age and Delta REM Sleep Measures with Scopolamine Treatment

	Correlation Coefficient
FIRST REM EPISODE	
REM latency	0.46
REM activity	−0.28
REM density	0.30
REM duration	−0.30
ALL REM EPISODES	
REM activity	−0.14
REM density	0.20
REM duration	−0.60*
Number of REM episodes	−0.54
REM sleep (%)	−0.56

*$p \leq .05$.

DISCUSSION

To our knowledge, this is the first study to directly compare and contrast REM sleep responses to a pharmacologic challenge simultaneously in adolescents and adults. Moreover, we are not aware of any studies exploring the effects on the recovery night following a single dose of scopolamine administration. For the most part, scopolamine delayed the onset of REM sleep, as well as suppressed REM sleep and phasic REM activity to comparable extent in both adolescents and adults. Furthermore, rebound effects were comparable in the two groups. There were, however, subtle developmental differences. Younger subjects tended to show less REM sleep suppression with scopolamine administration, specifically with respect to tonic REM sleep measures. There was also a tendency for the adolescents to demonstrate greater degree of rebound effects on the recovery night, particularly on phasic REM sleep measures. These results suggest that the muscarinic cholinergic systems appear mature by adolescence. Therefore, the relatively normal REM latency observed in depressed adolescents does not appear to be due to the inability of normal adolescents to mount REM sleep changes in response to cholinergic agents.

Basic and clinical studies have demonstrated the involvement of muscarinic cholinergic systems in the regulation of REM sleep (George et al. 1974; Hobson et al. 1993; Jones 1993; Shiromani and Gillin 1987). While acute administration of muscarinic agonists can shorten REM latency, increase REM activity and REM density, and reduce slow-wave sleep (Berkowitz et al. 1990; Riemann and Berger 1989; Riemann et al. 1988; Sitaram and Gillin 1980; Sitaram et al. 1977, 1978), acute administration of muscarinic cholinergic antagonists generally produce the opposite effects (Gillin et al. 1991b; Hohagen et al. 1994; Poland et al. 1989, 1997; Sagalés et al. 1969; Salin-Pascual et al. 1993; Sitaram et al. 1978). Based upon the pharmacologic profile of the compounds used to manipulate sleep, it appears that both M1 and M2 muscarinic receptor subtypes are involved in the regulation of REM sleep and its various elements (Gillin et al. 1993; Imeri et al. 1994; Velazquez-Moctezuma et al. 1989, 1991; Zoltoski et al. 1993).

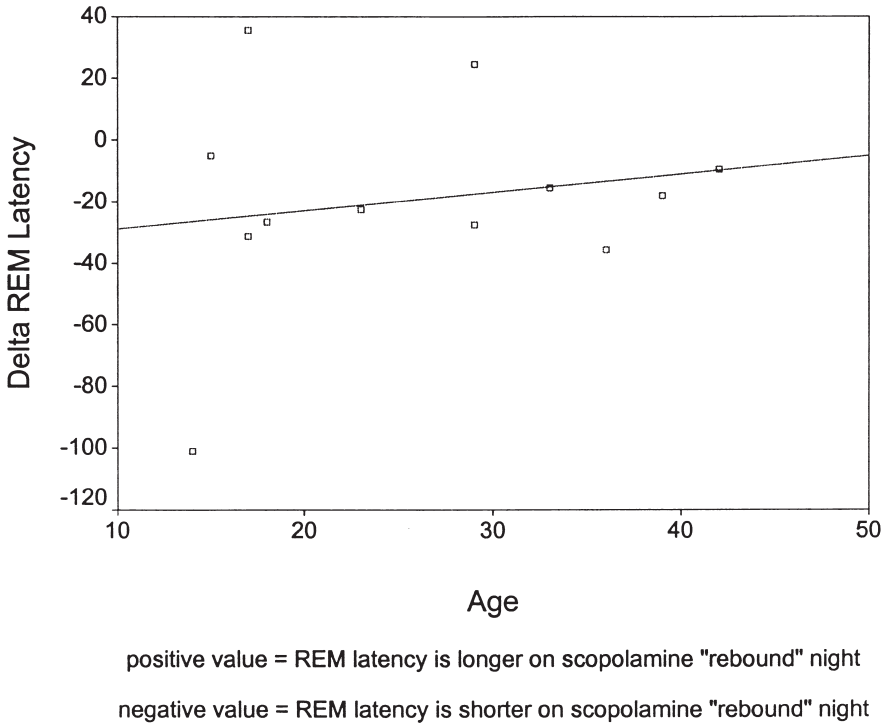

Figure 1. Delta REM latency (REM latency on the scopolamine-rebound night—REM latency on the placebo-rebound night) on the rebound night following scopolamine treatment.

The results from this study should be considered as preliminary findings due the modest sample sizes of the two groups. Despite this limitation, the study extends other reports showing a consistency between youngsters and adults in REM sleep changes on administration of cholinergic agents and antidepressants with strong anticholinergic properties (Dahl et al. 1994; Kupfer et al. 1979; McCracken et al. 1997; Shain et al. 1990).

Developmental differences in the suppression of tonic REM sleep measures in the context of comparable age-related effects on the phasic REM measures suggest that the neuro-regulatory systems controlling these two aspects of REM sleep may be different, and may mature at different rates (Cabeza et al. 1994; Siegel 1994). Lauer et al. (1991), examining developmental differences in EEG sleep changes in depressed patients, noted that REM density is relatively unaffected by age and that it may be a more consistent psychobiological marker for depression. We also found higher REM activity and REM density in adolescent depressed patients with no evidence of reduced REM latency (McCracken et al. 1997).

The subtle developmental differences in the REM sleep responses to scopolamine observed in the present investigation support previous reports of age-related differences in hypothalamic-pituitary-adrenal response to cholinergic challenge and in muscarinic receptor binding in animals (McCracken and Poland 1990; Sutin et al. 1986), as well as developmental differences in the prevalence of neuroleptic-induced acute dystonic reactions (Keepers et al. 1983). In order to further clarify the nature and extent of developmental differences in the cholinergic regulation of REM sleep during normal development and in depression, future investigations should include larger samples of both normal controls and depressed patients from various age groups, including younger children. In addition to the cholinergic systems, REM sleep regulation may also involve the aminergic systems (McCarley and Massaquoi 1992; McCarley et al. 1995; Myers et al. 1993). Future studies also should focus on the aminergic and cholinergic systems simultaneously (Seifritz et al. 1998) both in adults and in juvenile populations.

In summary, these preliminary results do not support the hypothesis that substantial developmental differences in the cholinergic regulation of REM sleep may be associated with reduced prevalence of REM sleep abnormalities in depressed adolescents. There are, however, minor developmental differences in some REM sleep measures. As opposed to a primary dysregulation of the cholinergic neurotransmission, developmental variations in other neuro-regulatory systems controlling REM sleep should be explored in the future.

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