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The Effect of Δ^9-Tetrahydrocannabinol on Sleep

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Abstract. Five volunteers slept 8 to 15 consecutive nights in the laboratory with electroencephalogram, chin electromyogram, and eye movements monitored by the method originated by Dement and Kleitman. Δ^9-tetrahydrocannabinol (THC), 20 mg administered at bedtime decreased the amount of time spent in the REM or paradoxical phase of sleep. Abrupt withdrawal of THC after 4 to 6 consecutive nights of use produced a mild insomnia characterized by difficulty in falling and staying asleep but did not produce a marked REM rebound.

Key words: Δ^9-Tetrahydrocannabinol — THC — Marihuana — Sleep — REM State — EEG.

Introduction

All-night polygraphic studies have shown that many psychoactive drugs have a characteristic effect on sleep. Acutely these agents depress the percentage of the total sleep time spent in the rem or paradoxical stage of sleep. With chronic administration of these agents this REM suppression is lost and the REM percentage climbs back to its baseline levels. When these drugs are abruptly discontinued after chronic administration sleep becomes characterized by frequent awakenings, a long sleep latency, and a marked increase in the REM percentage, the so-called REM rebound. When given for one night Δ^9-tetrahydrocannabinol (THC), the major psychoactive agent of marihuana, causes a moderate REM suppression (Pivik *et al.*, 1972). The present study reports the effect on polygraphically monitored sleep of the chronic administration of THC. A number of abstracts concerning the chronic effect of marihuana in human sleep have appeared (Karacan *et al.*, 1972; Kales *et al.*, 1972; Freemon, 1972a; Gillin *et al.*, 1972; Pranikoff *et al.*, 1973).

Method

Subjects. Six paid volunteers between the ages of 21 and 29 slept in the laboratory in pairs. Previous experience with marihuana consisted of occasional social use except for subject F who had used marihuana heavily, almost daily, between ages 16 and 18. This subject had also used LSD during this period; no other subject had used illegal drugs other than marihuana. Subjects A and B, who smoked marihuana about one Saturday night per month, abstained from its use for six weeks prior to the study. Other subjects professed they had not used marihuana for over one year.

Procedure. Polygraphic monitoring of electroencephalogram, eye movements and chin electromyogram was performed by the methods developed by Dement and

Kleitman (1957) and codified by Rechtschaffen and Kales (1968). All subjects slept in the laboratory for at least one night prior to the beginning of the study for acclimation to the technical apparatus. During the experiment, subjects A and B slept 8 consecutive nights in the lab; the other subjects slept 14 consecutive nights. On each night the subjects reported to the laboratory between 2200 and 2230 and were prepared and in bed by 2300. They drank 20 ml of juice while in bed just before the lights were turned off and the experiment begun. For subjects A and B this carrier was prune juice; for the others it was Lipomul (Upjohn), a mixture of corn oil and other fatty substances. On certain nights, indicated in the tables by asterisks, 20 mg of THC was dissolved in the carrier. The subjects and the technician were unaware of the schedule of active and inactive substances. As a control for consecutive night effects, subject C received no THC though she believed herself to be receiving THC on some nights.

After discarding the first night in the series, the records were scored by rigorous observation of the scoring criteria of Rechtschaffen and Kales (1968) without knowledge of experimental conditions. Because REM sleep is not homogeneously distributed, sleep stage percentages were calculated for the first 6 h of sleep (see Freemon, 1972b).

Drug. The Δ^9-tetrahydrocannabinol was supplied by the Center for Studies of Narcotic and Drug Abuse, National Institute of Mental Health. The project had the approval of the Milwaukee County Institutions Research Committee, the Wisconsin Dangerous Substances Control Committee, the Tennessee Department of Mental Health, the Food and Drug Administration, The United State Bureau of Narcotics and Dangerous Drugs, and the FDA-NIMH Psychotomimetic Agents Advisory Committee.

Results

In each of the five subjects who received THC, the percentage of sleep spent in the REM state was less on the first THC night than on baseline nights. In the two subjects who took THC for four consecutive nights, the REM percentage remained depressed throughout this period. In the three subjects who took THC for six consecutive nights, the REM percentage remained depressed in subject D but in the other two the REM percentage returned to baseline levels, actually somewhat above baseline levels, while the THC was still being administered. Table 1 summarizes these results.

The post-THC or THC withdrawal period was not associated with a REM rebound; that is, the REM percentage during the first few post-THC nights was not generally greater than baseline REM percentages. Subject A had a very early onset REM period, only 6 min after the first sleep spindle announced sleep onset, on the second post-THC night but no other subject showed such a short REM latency. The only evidence for a withdrawal effect was the tendency in some subjects for an increased sleep latency (time from lights out and the subject saying "good night" to the first sleep spindle) and time awake (awake time as defined by polygraphic criteria between the first onset of sleep and the conclusion of the experiment after 6 h of sleep). Subject B had a sleep latency of 30 min and subject E of 40 min on the first or second withdrawal nights. All five of subject F's withdrawal nights had a greater sleep latency than

Table 1. Percentage of the total sleep time spent in the REM state

	REM Percentage					
	A	B	C	D	E	F
2	27.9	22.9	23.3	19.3	22.8	18.1
3	24.6[a]	20.9[a]	20.0	21.1	20.7	18.6
4	21.1[a]	18.7[a]	19.2	14.0[a]	15.5[a]	17.8[a]
5	15.5[a]	18.4[a]	28.2	19.6[a]	16.7[a]	14.7[a]
6	14.9[a]	15.1[a]	22.4	16.0[a]	22.8[a]	13.7[a]
7	29.2	16.8	25.2	14.3[a]	21.5[a]	16.8[a]
8	21.3	23.6	23.6	16.3[a]	26.8[a]	20.6[a]
9			23.8	14.8[a]	25.1[a]	23.7[a]
10			22.9	19.1	22.7	22.4
11			26.8	25.2	20.4	17.6
12			22.4	20.3	23.4	16.8
13			25.0	18.7	22.6	19.5
14			26.0	20.4	18.6	24.9

[a] 20 mg of THC administered.

Table 2. REM latency in minutes, defined as the time between the first sleep spindle and the beginning of the first REM period

	REM Latency					
	A	B	C	D	E	F
2	69	55	62	134	79	116
3	48[a]	64[a]	58	74	66	80
4	66[a]	69[a]	53	103[a]	67[a]	57[a]
5	54[a]	72[a]	67	61[a]	72[a]	55[a]
6	56[a]	128[a]	118	116[a]	60[a]	67[a]
7	64	70	106	102[a]	78[a]	105[a]
8	6	60	64	72[a]	74[a]	74[a]
9			61	61[a]	70[a]	80[a]
10			45	70	70	90
11			46	102	62	57
12			68	53	65	165
13			53	36	63	62
14			52	41	66	90

[a] 20 mg of THC administered.

either baseline night. Four of the 5 subjects had a greater time awake on one of the first two post-THC nights than on a baseline night. Subject D had a waking time on four of the five post-THC nights greater than either baseline night. Tables 2, 3, and 4 summarize these results.

Other variables measured but showing no definite changes from baseline values included the duration of each non-REM substage, the total sleep time, and the number of times per night the subject awakened or roused to non-REM stage 1 from a deeper stage. Because some drugs affect

Table 3. Sleep latency in minutes, defined as the time between lights out and the first sleep spindle

	Sleep latency					
	A	B	C	D	E	F
2	8	6	8	13	13	8
3	9[a]	11[a]	7	27	6	10
4	5[a]	8[a]	5	9[a]	13[a]	9[a]
5	5[a]	11[a]	13	16[a]	9[a]	13[a]
6	4[a]	5[a]	14	16[a]	24[a]	6[a]
7	11	30	15	12[a]	6[a]	12[a]
8	9	6	16	15[a]	31[a]	5[a]
9			9	24[a]	13[a]	7[a]
10			15	22	9	21
11			13	10	40	14
12			12	11	13	12
13			12	22	24	13
14			20	20	6	16

[a] 20 mg of THC administered.

Table 4. Waking time in minutes, defined as the time spent awake as defined by the polygraphic criteria after the first sleep spindle

		Waking time					
		A	B	C	D	E	F
	2	5	2	12	4	2	14
	3	9[a]	4[a]	46	2	3	5
	4	6[a]	11[a]	34	1[a]	0[a]	1[a]
	5	7[a]	18[a]	11	3[a]	15[a]	1[a]
	6	1[a]	1[a]	47	22[a]	0[a]	0[a]
N	7	7	16	5	4[a]	1[a]	0[a]
I	8	18	6	15	12[a]	3[a]	3[a]
G	9			43	13[a]	0[a]	1[a]
H	10			23	39	0	2
T	11			10	31	7	0
	12			33	0	0	3
	13			30	18	9	3
	14			8	19	1	0

[a] 20 mg of THC.

only part of a night's sleep the length of each non-REM and REM period was examined and all variables were calculated on the basis of each two hours of sleep, but again, no definite changes associated with THC administration or THC withdrawal were apparent. Since Pivik *et al.* (1972) found that THC increased non-REM stage 4 and Pranikoff *et al.* (1973) reported that street marihuana decreased stage 4, Table 5 presents the percentage of this substage on each night in this study.

Table 5. The percentage of the total sleep time spent in non-REM stage 4

		Non-REM Stage 4					
		A	B	C	D	E	F
	2	21.3	12.0	23.4	14.2	18.2	5.0
	3	24.4[a]	8.6[a]	14.9	18.9	23.9	16.2
	4	29.1[a]	13.9[a]	22.6	17.7[a]	26.4[a]	23.1[a]
	5	25.7[a]	9.2[a]	19.9	14.9[a]	29.4[a]	18.2[a]
	6	12.1[a]	13.3[a]	21.0	11.8[a]	23.4[a]	21.1[a]
N	7	20.4	8.1	10.4	15.1[a]	17.3[a]	16.8[a]
I	8	15.9	10.3	22.6	14.5[a]	16.3[a]	21.9[a]
G	9			11.3	5.4[a]	21.6[a]	19.5[a]
H	10			9.5	17.4	15.9	15.1
T	11			11.5	14.4	14.8	21.1
	12			16.0	13.5	19.2	21.4
	13			18.2	9.4	18.2	19.9
	14			14.1	13.5	20.3	20.7

[a] 20 mg of THC.

The subject who received no THC had no discernible changes in polygraphically monitored sleep during the course of the experiment. She proved to be a rather poor sleeper with generally prolonged sleep latencies and high awake times, both of these values were no greater during the "post-THC" period than on any other nights.

Discussion

A statistical analysis of polygraphic sleep research data can be difficult because each night cannot be treated as an independent entity (Oswald, 1973). A drug may have more, or in a few cases, less of an effect the first night it is given than after three or four nights of consecutive use. The REM percentage was less on the first THC night in each of these subjects than on any baseline for that subject. The probability of this occurrence is 1 in 32 times (P less than 0.05). However, there is considerable individual variation in the normal amount of REM percentage and in some cases the REM percentage is only very slightly less on the first THC night than on baseline nights so that Chi square analysis fails to show statistical significance for this effect. In only two subjects was the lowest REM percentage on the first THC night. In one subject it was on the third night and in two subjects the fourth night. If one extracts for each subject his two lowest REM percentage one finds that 9 out of these 10 nights occurred while the subjects were taking THC; the only exception is the first withdrawal night in subject B. Probability analysis shows that the likelihood of occurrence 9 of 10 lowest REM percentage nights on the experimental THC nights is less than 1 in 1000. Though the statistical analysis of this type of data is difficult it does seem that we can conclude without much equivocation that the present study confirms the previous

findings of Pivik and his *co-workers* (1972) that THC decreases the percentage of sleep time spent in the REM type of sleep. In this effect THC resembles a large diverse group of psychoactive agents including alcohol, barbiturates, other sedatives and depressants, as well as amphetamine and other agents. In this effect on sleep THC differs from LSD which increases REM sleep time (Muzio *et al.*, 1967).

Unlike most REM suppressing drugs, however, THC does not produce a clear increase in REM sleep when it is withdrawn after 4 to 6 consecutive nights of use. According to interviews conducted by the National Commission on Marihuana and Drug Abuse (1972) many chronic marihuana users experienced mild insomnia when they attempted to discontinue the use of marihuana. The objective polygraphic correlates of these subjective reports are the increased waking and prolonged sleep latencies seen in some subjects of this study. Failure to demonstrate a clear REM rebound in these subjects may be related to the slow metabolism of THC. THC is stored in fat (Kreuz and Axelrod, 1973) and its metabolites are recovered in urine and feces for several days after administration (Lemberger *et al.*, 1971). This slow elimination of THC may produce such a gradual decline of THC and its metabolites that no really acute withdrawal can occur.

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