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Suppression of REM and Delta Sleep by Apomorphine in Man: A Dopamine Mimetic Effect

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Abstract. Apomorphine, a direct stimulant of dopamine receptors, was given in nonemetic doses by continuous IV infusion for 180 – 240 min during night sleep in normal subjects. During apomorphine infusion, a significant reduction of stage (S)4 and an abolition of rapid eye movement (REM) sleep occurred. The percent duration of S2 was significantly increased. In the 240 min following interruption of a 240-min infusion of apomorphine, a significant increase of S4 and REM percent duration was observed. The effect of apomorphine infusion on sleep was prevented by the administration of haloperidol or sulpiride, two dopamine receptor blocking agents. This suggests that it is due to a dopamine mimetic action.

Key words: REM sleep – Delta sleep – Apomorphine – Dopamine

There is evidence that brain catecholamines (CA) play an important role in the regulation of sleep in humans. Inhibition of CA synthesis with alpha-methyltyrosine or with alpha-methylphenylalanine has been shown to increase the proportion of rapid eye movement (REM) sleep (Wyatt et al., 1971). On the other hand, administration of L-dopa, the immediate precursor of dopamine (DA), decreased REM sleep (Wyatt et al., 1970). Moreover, IV infusion of L-dopa during non-REM (NREM) sleep delayed the onset of REM sleep, while its infusion at REM sleep onset shortened the duration of this stage (Gillin et al., 1973).

However, the results of these studies do not permit differentiation of the relative roles of DA and norepinephrine (NE), since the treatments used influence the metabolism of both amines (Spector et al., 1965; Gershon et al., 1970; Wurtman and Romero, 1972). Moreover, L-dopa also affects serotonin metabolism (Everett and Borcherding, 1970). We felt that more information about the specific role of DA in regulation of sleep mechanisms could be obtained by using apomorphine (AP) a direct stimulant of DA receptors (Ernst, 1967; Andén et al., 1967; Creese et al., 1975).

We report here that the infusion of AP in nonemetic doses suppresses REM sleep and markedly reduces delta sleep. Moreover we show that the AP effect is prevented by haloperidol and sulpiride, two specific inhibitors of DA receptors (Tagliamonte et al., 1975; Restelli et al., 1975; Elliot et al., 1977).

Materials and Methods

The night sleep of 18 subjects (ten females and eight males), unaffected by brain diseases and free from drugs for at least 14 days, was studied by continuous electroencephalogram (EEG), horizontal electrooculogram (EOG), and submental electromyogram (EMG) recording. Subjects gave proper consent for the experimentation. Each slept in an acoustically attenuated room and initially underwent two nights of sham registration to adapt to the conditions of the experiment.

The experiment consisted of two parts. In the first, ten subjects (six females and four males, ages 22 – 40 years, and body weights of 38 – 78 kg) were infused IV for 180 min with AP in nonemetic doses (10 – 15 μg/min) or placebo, randomly, at 2-day intervals. In the second part of the experiment, eight subjects (four females and four males, ages 21 – 34 years, and body weights 41 – 70 kg) were also infused for 240 min with IV AP (8 – 12 μg/min) or placebo in random succession. However, 5 min prior to the infusion, 2 ml placebo IM or a DA receptor blocking agent IM was administered. The DA receptor blocking agent was haloperidol (2 mg) in four subjects (two females and two males) and sulpiride (100 mg) in the other four subjects. For each subject the pattern of treatment was as follows: Night A, placebo infusion preceded by placebo IM (eight subjects); night B, AP infusion preceded by placebo IM (eight subjects); and night C, placebo infusion preceded by IM haloperidol (first four subjects) or sulpiride IM (last four subjects) (Fig. 2). The succession of treatment varied randomly for each subject. There was a 3-day interval between experimental nights to avoid any residual effect.

Each night, AP or placebo infusions were stopped after 240 min. However, the infusion tubing was left in the vein and the subject was

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Table 1. Effect (mean ± SD., paired *t*-tests) of apomorphine infusion (180 min) on sleep patterns ($N = 10$)

	Placebo		Apomorphine	
	Minutes	Percent of sleep stages	Minutes	Percent of sleep stages
Sleep onset latency	26.1 ± 8.3	–	22.4 ± 14.2	–
Interspersed wakefulness	8.0 ± 8.2	–	19.1 ± 18.9	–
Stage 1 (NREM)	10.6 ± 4.1	7.3 ± 2.8	17.3 ± 7.1	12.5 ± 5.1[a]
Stage 2 (NREM)	54.2 ± 16.8	37.1 ± 11.5	95.0 ± 27.9	68.6 ± 20.1[b]
Stage 3 (NREM)[d]	22.1 ± 10.4	15.2 ± 7.2	18.8 ± 17.2	13.6 ± 12.4
Stage 4 (NREM)[d]	44.8 ± 16.9	30.7 ± 11.6	7.4 ± 13.1	5.3 ± 9.4[c]
REM	14.2 ± 12.5	9.7 ± 8.5	0.0 ± 0.0	0.0 ± 0.0[b]

[a] $P < 0.05$
[b] $P < 0.01$
[c] $P < 0.001$
[d] Percent delta sleep (S3 + S4) during placebo was 45.9 ± 17.7 and during apomorphine, 18.9 ± 19.8; the difference is significant ($P < 0.01$)

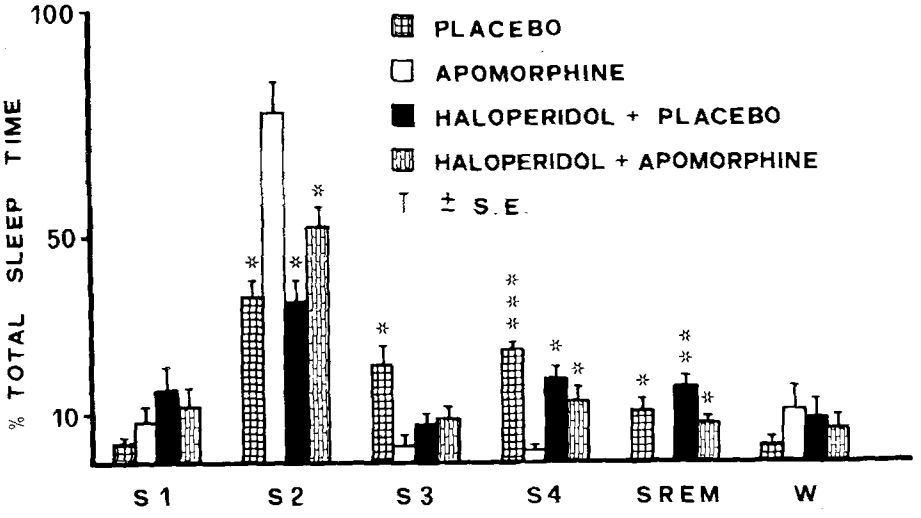

Fig. 1. Effect of haloperidol pretreatment on sleep during apomorphine. *S1*, *S2*, *S3*, *S4*, and *SREM* indicate stages (S) of sleep. *W* indicates interspersed wakefulness. Columns refer to the four types of treatment: Placebo infusion preceded by placebo IM; apomorphine infusion preceded by placebo IM; placebo infusion preceded by haloperidol IM; and apomorphine infusion preceded by haloperidol IM. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ (paired *t*-tests). Each value is the mean ± SE of four subjects

not awakened so the EEG polygraphic recording continued until spontaneous awakening of the subject.

Apomorphine HCl was freshly dissolved in saline (containing ascorbic acid 0.5 mg/ml as antioxidant) at the concentration of 10^{-4} M. The solution was infused with an infusion pump at a constant rate using a polyethylene tube 10 feet in length which extended from the subject's forearm to an observation room outside the subjects' room. Placebo consisted of a solution of 0.5 mg/ml ascorbic acid in saline.

Sleep stages and wakefulness were codified, according to international standard scoring criteria (Rechtschaffem and Kales, 1968), by an examiner who was unaware of the drug administered. *t*-Tests for matched pairs were used for evaluating the results.

Results

The results obtained in the ten subjects of the first part of the experiment are shown in Table 1. During 180 min of AP infusion, a significant reduction of stage (S)4 and abolition of REM sleep occurred. The duration of S2 and S1 were proportionally increased. Thus, the EEG pattern during AP infusion was characterized almost exclusively by the presence of "light" sleep. Sleep onset latency did not significantly differ from placebo nights.

The results of the second part of the experiment are shown in Fig. 1 (four subjects with haloperidol pretreatment) and in Table 2 (four subjects with sulpiride pretreatment). In these eight subjects the effects of AP infusion on sleep were similar to those of the ten subjects in the first part of the experiment, i.e., abolition of REM sleep and dramatic reduction of S4 and S3 sleep were noted, while S2 was proportionally increased. The administration of haloperidol or sulpiride did not significantly modify sleep parameters compared to placebo nights. However, the pretreatment with these drugs antagonized the effects of AP, restoring a sleep pattern similar to that during placebo or during placebo preceded by the DA receptor blocking drugs. Typical sleep patterns of one subject in the four experimental conditions are shown in Fig. 2.

The effect observed on stage duration and latency in the 240 min following interruption of 240 min AP infusion (without inhibitors) are illustrated in Tables 3

Table 2. Effect (mean ± SD, paired *t*-tests) of pretreatment with sulpiride on sleep during apomorphine infusion ($N = 4$)[a]

	IM placebo + placebo infusion		IM placebo + apomorphine infusion		IM sulpiride + placebo infusion		IM sulpiride + apomorphine infusion	
	Minutes	Percent stages of sleep	Minutes	Percent stages of sleep	Minutes	Percent stages of sleep	Minutes	Percent stages of sleep
Sleep onset latency	33.3 ± 13.4	–	19.5 ± 8.8	–	25.8 ± 11.0	–	25.8 ± 14.0	–
Interpersed wakefulness	8.5 ± 10.3	–	8.6 ± 9.0	–	9.4 ± 5.8	–	7.9 ± 10.7	–
Stage 1 (NREM)	10.1 ± 4.5	5.1 ± 2.3	12.8 ± 6.4	6.0 ± 3.0	13.3 ± 5.8	6.5 ± 2.8	11.1 ± 8.1	5.4 ± 3.9
Stage 2 (NREM)	88.5 ± 6.4[b]	44.7 ± 3.2[b]	174.0 ± 38.8	82.1 ± 18.3	94.3 ± 12.8[b]	46.0 ± 6.3[b]	105.0 ± 16.5	50.9 ± 8.0
Stage 3 (NREM)	29.1 ± 13.0	14.7 ± 6.6	21.6 ± 30.0	10.2 ± 13.9	40.7 ± 17.6	19.9 ± 8.6	42.4 ± 12.6	20.6 ± 6.1
Stage 4 (NREM)	55.0 ± 19.8[c]	27.7 ± 10.0[c]	3.5 ± 7.0	1.7 ± 3.3	37.9 ± 14.3[b]	18.5 ± 7.0[b]	30.4 ± 11.6	14.7 ± 5.6
REM	15.5 ± 4.1[c]	7.8 ± 2.1[c]	0.0 ± 0.0	0.0 ± 0.0	18.6 ± 5.1[c]	9.1 ± 5.5[c]	17.4 ± 6.2[b]	8.4 ± 3.0[b]

[a] Statistical evaluations are all in comparison with IM placebo + apomorphine infusion
[b,c] Significantly different at $P < 0.05$ and $P < 0.01$ level, respectively

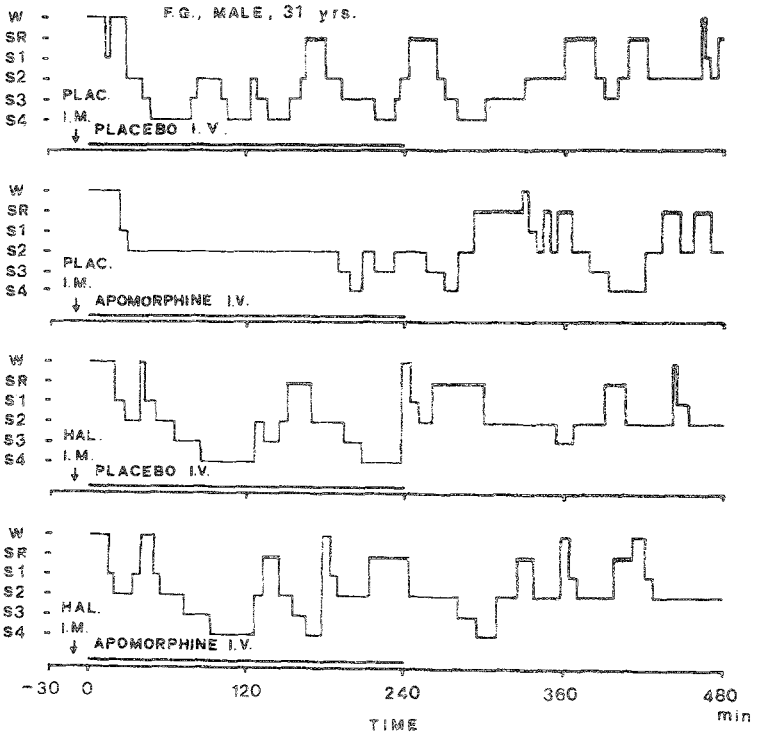

Fig. 2. Sleep patterns during the four types of treatment in one subject. Sleep stages are indicated on the left: (*SR*) stage (*S*) REM; (*W*) interspersed wakefulness; (*Plac*) placebo; and (*Hal*) haloperidol. The period of infusion of placebo or apomorphine (240 min) is indicated by the horizontal line

and 4. A significant increase of S4 and REM percent duration was observed. Moreover, the latencies of S4 and S3 sleep were significantly reduced.

Discussion

Infusion of nonemetic doses of AP markedly depressed S4 and totally suppressed REM sleep. Sleep during AP infusion showed, therefore, prevalently a "light" sleep.

Discontinuation of AP was associated with an elevation of S4 and REM sleep, which might indicate a rebound phenomenon due to the preceding suppression.

AP-Induced changes in sleep patterns are prevented by haloperidol and sulpiride pretreatment, indicating that they are mediated by the stimulation of DA receptors. The latter seem to be different from the "self-inhibitory" DA receptors, or "autoreceptors" (Bunney and Aghajanian, 1975), whose activation inhibits dopaminergic transmission, since AP effects are opposite to those observed in humans treated with specific inhibitors of CA biosynthesis (Wyatt et al., 1971) and quite different from those treated with DA receptor

Table 3. Percent duration of single stages during 240 min following interruption of apomorphine or placebo infusion[a]

	After 240 min placebo		After 240 min apomorphine	
	Minutes	Percent	Minutes	Percent
Wakefulness	11.0 ± 11.5	4.6 ± 4.8	6.7 ± 4.6	2.8 ± 1.9
Stage 1 (NREM)	4.8 ± 4.3	2.0 ± 1.8	2.2 ± 2.4	0.9 ± 1.0
Stage 2 (NREM)	116.2 ± 30.3	48.4 ± 12.6	95.5 ± 22.3	39.8 ± 9.3
Stage 3 (NREM)	26.9 ± 38.4	11.2 ± 16.0	28.1 ± 10.6	11.7 ± 4.4
Stage 4 (NREM)	16.1 ± 15.6	6.7 ± 6.5	34.1 ± 7.4	14.2 ± 3.1[b]
REM	65.0 ± 17.1	27.1 ± 7.1	73.4 ± 17.5	30.6 ± 7.3[b]

[a] Each value is the mean ± SD from eight subjects
[b] $P < 0.05$

Table 4. Latency[a] to single stages (min) following interruption of 240 min apomorphine or placebo infusion

	Placebo	Apomorphine
Latency to stage 1	132.3 ± 107.6	153.4 ± 100.1
Latency to stage 2	35.4 ± 37.5	20.3 ± 19.6
Latency to stage 3	118.0 ± 91.7	39.5 ± 27.4[b]
Latency to stage 4	152.4 ± 79.6	56.8 ± 34.9[b]
Latency to REM	35.2 ± 33.7	45.2 ± 26.4

Each value is the mean ± SD from eight subjects
[a] Latencies were calculated from the time of interruption to the onset of a given stage. Therefore, it was considered zero for the stage which was present at the time of infusion interruption. When a single stage did not occur during the 240 min of registration, the latency value was computed as 240
[b] $P < 0.05$

blockers (Schneider et al., 1975; Sagales and Errill, 1976).

On the other hand, the effect of AP resembles that obtained with L-dopa administration. In fact, according to Gillin et al. (1973), when infused during the first NREM period, L-dopa delayed the onset of the first REM period, while when infused at REM onset it shortened the length of the REM period. However, unlike AP, L-dopa infusion was not found to decrease the delta phases of sleep (Gillin et al., 1973). This also did not occur with oral L-dopa administration, which was found to have REM suppressive effects in depressed patients (Fram et al., 1970) and at high doses in parkinsonians (Bergonzi et al., 1974), although not in normal subjects (Azumi et al., 1972; Nakazawa et al., 1973).

The difference may be due to the fact that AP action on DA receptors is quite specific (Andén et al., 1967; Ernst, 1967; Creese et al., 1975), whereas L-dopa not only increased DA concentration, but also affected NE (Gershon et al., 1970; Wurtman and Romero, 1972) and serotonin metabolism (Everett and Borcherding, 1970).

Owing to the low efficacious doses of AP, it is possible that DA receptors responsible for AP and L-dopa responses are a special kind of post-synaptic DA receptor, sensitive to lower concentrations of the transmitter than the classic post-synaptic DA receptors involved in regulation of the extrapyramidal functions.

Our results with humans completely differ from those obtained with AP in rats. In fact, Benesova (1976) found no changes, while Mereu et al. (1979) found an increase in REM as well as total sleep with a single IP dose of AP (100 µg/kg). This is probably due to the different sleep mechanisms in lower mammals, where CA promote REM sleep and serotonin is associated with NREM sleep (Jouvet, 1969).

The S4 and REM stage suppression obtained with AP is followed by a marked increase of these stages after interruption of the drug infusion; the residual effect of the drug is very brief due to its very short half-life (about a few minutes). This rebound phenomenon seemed to be very similar to that observed after REM (Dement, 1960) or S4 (Bergonzi et al., 1972) deprivation by the awakening techniques.

Our results indicate that the dopaminergic system inhibits both REM and slower delta sleep. Interestingly, marked decreases in the amounts of REM and delta sleep have been noted in acute schizophrenia (Kupfer et al., 1970), a condition in which a DA hyperstimulation has been suggested (Snyder, 1973).

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