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Effect of 10 Days Reserpine or Apomorphine Administration on Sleep Cycles in Rats

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BENEŠOVÁ, O. *Effect of 10 days reserpine or apomorphine administration on sleep cycles in rats.* PHARMAC. BIOCHEM. BEHAV. 4(2) 119–122, 1976. – The duration of sleep-wakefulness periods and sleep cycles was investigated by means of EEG and EMG in rats with implanted brain electrodes and myographic electrodes in neck muscles during 5 hr trials after repeated administration of 2 depressant drugs, reserpine and apomorphine. Ten days administration of reserpine at a dose of 0.05 mg/day, SC, decreased the duration of both slow-wave and paradoxical sleep, whereas apomorphine had no effect on sleep duration or occurance of sleep phases in either the low dose (0.2 mg/kg/day, SC) or in the high dose of 0.6 mg/kg/day, SC. This finding might be correlated with previously found differences in catecholamine levels in the brain in the same model experiments.

Apomorphine Reserpine Sleep cycles Depressant drugs

CLINICAL experience has shown that repeated administration of reserpine or apomorphine in small doses induces a depressive state in men [7, 17, 18]. In our laboratory, we have studied the action of both these depressant agents in model experiments in rats and have demonstrated some differences in their effects. Ten days administration of reserpine or apomorphine in small subcutaneous doses depressed the motility of rats, decreased the level of acetylcholine in the diencephalon and increased the activity of tryptophanepyrrolase in the liver [2,10] But simultaneously, differences in catecholamine levels in the brain were found. Reserpine treatment led to a significant decrease of noradrenaline and dopamine in the brain, whereas apomorphine caused an increase in both catecholamines [1].

In the present study, we investigated the effect of both reserpine and apomorphine on sleep cycles in rats, regarding the fact that human psychotic depression is usually associated with sleep disturbances [11,13].

METHOD

Animals and Surgery

Our experiments were carried out on 26 male rats (average body weight of 350 g) with implanted brain electrodes and a myographic electrode in the neck muscle. For cortical electrodes we used nickel plated screws of 1 mm dia., 2 implanted into the skull in the frontal area (one on the right, one on the left hemisphere) and 2 similarly in the occipital area. The subcortical electrodes were bipolar (tips distance 0.5 mm), made from enamelled constantan wire of 0.17 mm dia. and implanted into the hippocampus (AP 3, L 2.5–3, D 3) and thalamus (AP 2, L 1–1.5, D 5). All electrodes were connected to a miniature electrical plug-socket, fixed to the skull by dental cement. For the electrode placements, the stereotaxic atlas of the rat brain by Fifková and Maršala [3] was used.

Procedure

The implantation was performed under thiopenthal anestesia (60 mg/kg IP) and first sessions consisting of adaptation to the experimental situation (a minimum of 5 sessions of 30–60 min) were performed 14 days after the operation.

In these rats, freely moving in a box 30 × 33 cm, we recorded the occurance and duration of wakefulness, slow-wave and paradoxical sleep in 5 hr trials using EEG and EMG records and visually checked behavioral changes (Fig. 1).

In the first experiment, we used 3 groups of 5 animals each. One group was administered reserpine (Reserpin Spofa 2.5 mg/ml diluted with saline 1:100) for 10 days at a dose of 0.05 mg/kg SC, another received apomorphine (Apomorphin Spofa 5 mg/ml diluted with saline 1:50) at a dose of 0.2 mg/kg SC and the third received saline. On the eleventh day the registration of sleep cycles was carried out. Doses of both drugs used in this experiment may be correlated with human dosage.

A second experiment was performed according to the same schedule but using apomorphine, at a dose 3 times higher i.e., 0.6 mg/kg/day, SC. Six rats were administered apomorphine, 5 rats received saline.

The record of every rat from 5 hr experiment was evaluated with following determinations: (1) the duration of wakefulness, slow-wave and paradoxical sleep both in single hours and during the whole experiment; (2) number of sleep cycles (paradoxical sleep preceded by slow-wave sleep and wakefulness) and (3) total time of sleep (slow-wave

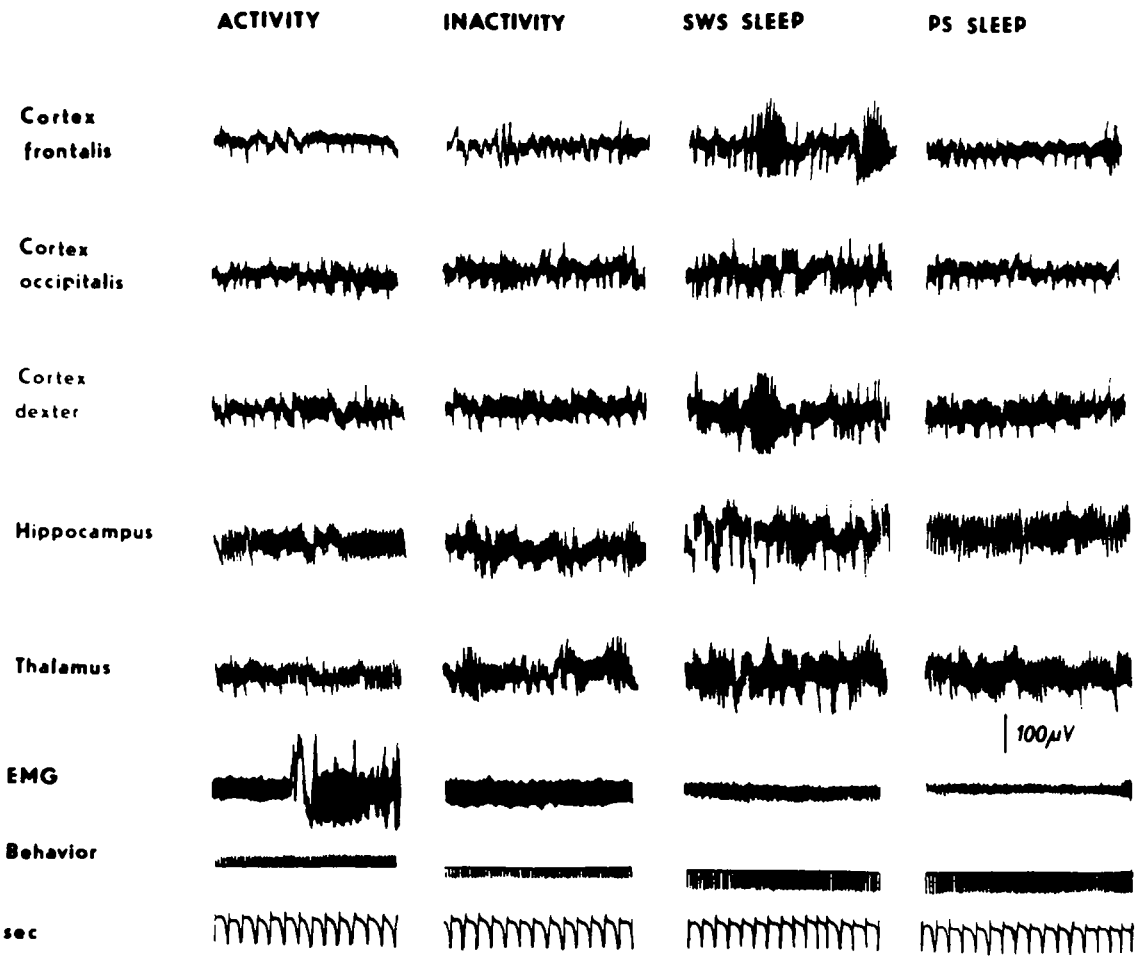

FIG. 1. Different stages of vigilance (activity, inactivity) and sleep (slow-wave sleep=SWS, paradoxical sleep = PS) in EEG and EMG (neck muscle) records. Behavioral activity was registered visually. Note the low amplitude–high frequency EEG activity in cortical leads, theta activity in the thalamus and hippocampus and relaxation in neck muscle EMG during paradoxical sleep.

sleep + paradoxical sleep). The means with 95% confidence limits were plotted for the groups and differences evaluated by using T-test.

RESULTS

Results from the first experiment (Fig. 2) show that the 10 days administration of reserpine (0.05 mg/kg/day SC) increased periods of wakefulness and decreased the duration of both slow-wave and paradoxical sleep, especially in the third hour of the observation. Statistically significant difference from the control group may also be seen in the columns representing the sum of the results from the whole 5 hr experiment. On the other hand, apomorphine (0.2 mg/kg/day SC) did not produce any change in sleep parameters from the values of control group.

Further analysis of the results is presented on the Fig. 3. After reserpine treatment, rats had a lower number of complete sleep cycles and decreased total sleep time. This last result is statistically highly significant. Apomorphine did not change any sleep parameter under observation with only the exception of a slightly increased number of sleep cycles in the 4th hour of experiment.

Results of a second experiment with apomorphine using a 3 times higher dose (0.6 mg/kg/day SC) indicated (Fig. 4) that this drug had no significant effect on sleep duration or occurrence of different sleep phases, even at this high dosage.

DISCUSSION

Our experiments have shown that 10 days administration of small doses of reserpine (0.05 mg/kg/SC) which are equivalent to the human therapeutic dosage disturbs sleep in rats in terms of decreasing both slow-wave and paradoxical sleep. These results are in agreement with prior data concerning a single dosage of reserpine in rats [6], in cats [5, 9, 12, 14] in rabbits [16] and in man [9]. Coulter *et al.* [4] described in man a decrease in slow-wave sleep, but an increase in REM sleep. Prolongation of REM sleep in monkeys was reported also by Reite *et al.* [15] and in man by Hartmann [8], but these authors used relatively high doses of reserpine. The effect of chronic administration of small doses of reserpine, modelling the depressant action of reserpine in the clinic – as it was used in our experiment – was not previously described. It is interesting to state that

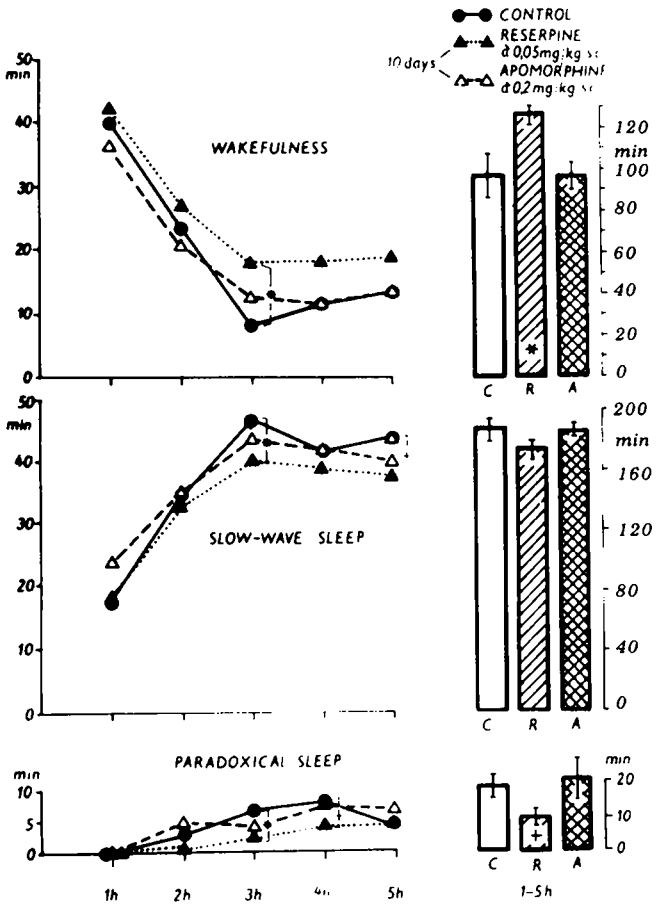

FIG. 2. The duration of wakefulness, slow-wave and paradoxical sleep in rats (5 animals per group) in the 5 hr experiment after 10 days administration of reserpine (0.05 mg/kg/day SC = R) or apomorphine (0.2 mg/kg/day SC = A) or saline (C). Vertical bars in columns represent 95% confidence limits of the mean. The arterisk denotes statistically significant difference at $p<0.05$, the cross at $p<0.1$.

the action of reserpine as a depressant drug was, in these model experiments, connected with sleep disturbances.

On the other hand, 10 days administration of another depressant agent – apomorphine – did not induce any sleep cycle changes. It is not excluded that these differences

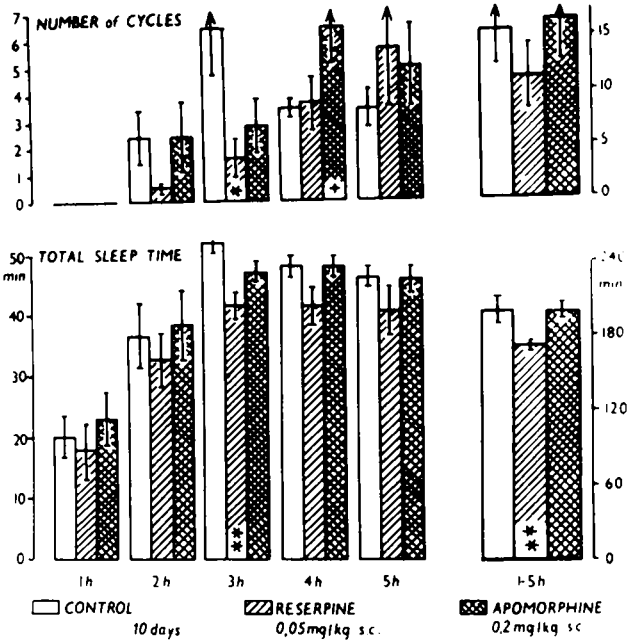

FIG. 3. Number of complete sleep cycles and the total time of sleep in male rats (5 animals per group) after 10 days administration of reserpine (0.05 mg/kg/day SC) or apomorphine (0.2 mg/kg/day SC) or saline. Vertical bars in columns represent 95% confidence limits of the mean. One arterisk denotes statistically significant difference at $p<0.05$, two arterisks at $p<0.01$, the cross at $p<0.1$.

might be related to differences in catecholamine levels in the brain as stated in our previous experiments [1,2].

All these results suggest that there are differences in the experimental model of the depressive state induced by reserpine and by apomorphine in animals. These differences seem also to have correlates in human trials since Tesařová [17] described the apomorphine induced depression as an inhibited, abulic one, whereas the clinical pattern of reserpine depression was dominated by symptoms of sadness of affect.

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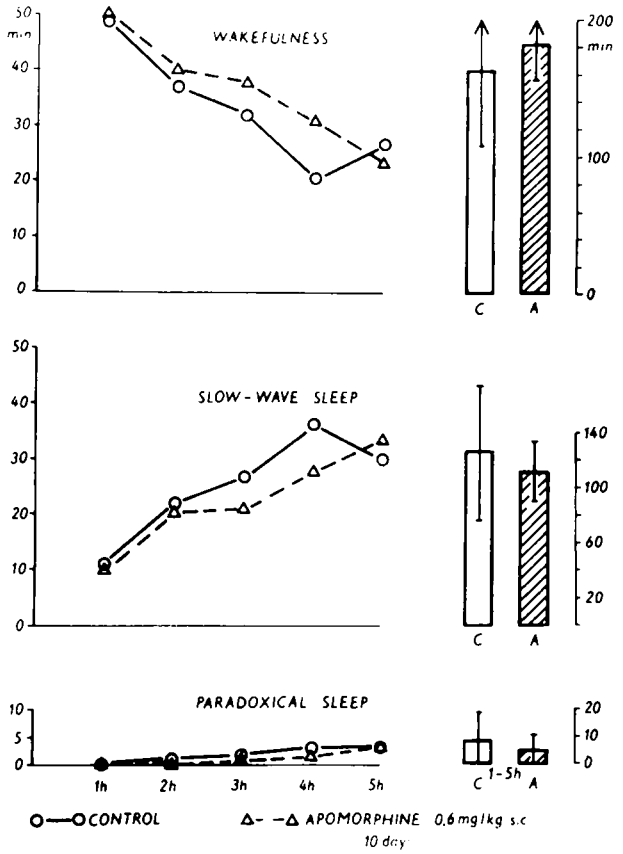

FIG. 4. The duration of wakefulness, slow-wave and paradoxical sleep in male rats during the 5 hr experiment after 10 days administration of apomorphine – A – at a dose of 0.6 mg/kg/day SC (6 animals) or saline (5 animals) – C. Vertical bars in columns represent 95% confidence limits of the mean.

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