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Rolipram, an Antidepressant That Increases the Availability of cAMP, Transiently Enhances Wakefulness in Rats

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LELKES, Z., P. ALFÖLDI, A. ERDŐS AND G. BENEDEK. *Rolipram, an antidepressant that increases the availability of cAMP, transiently enhances wakefulness in rats.* PHARMACOL BIOCHEM BEHAV **60**(4) 835–839, 1998.—A study was carried out on the effects on sleep of rolipram, an antidepressant that increases the availability of cAMP by inhibiting a phosphodiesterase isoenzyme. Rats were treated with rolipram (0.1 or 1 mg/kg) twice a day (at light and dark onset) for 11 days, after a chronic period of injection of physiological saline for habituation purposes. The sleep–wake activity was recorded for 12 h following the injection at light onset on the baseline day (physiological saline), on rolipram days 1, 5, and 11, and also on day 12, when physiological saline was injected again (withdrawal day). The high (1 mg/kg) dose of rolipram enhanced wakefulness (W) in postinjection h 1 on day 1 of rolipram treatment. After administration of 0.1 mg/kg rolipram, only a tendency to an increase in W was noted. The promotion of W might be attributed, at least in part, to an increased release of noradrenaline due to a cAMP-mediated stimulation of tyrosine hydroxylase. © 1998 Elsevier Science Inc.

Sleep Rolipram Phosphodiesterase inhibitor cAMP Antidepressant drugs

PATIENTS with depressive illness often complain of sleep disturbances characterized by poor sleep continuity, early awakening, diminished slow-wave sleep, and an abbreviated first non-REM sleep (NREMS) period, leading to a shortened REM sleep (REMS) latency (28). The fact that manipulations of the sleep–wake activity (sleep deprivation and phase advancement of the sleep–wake cycle) are effective in relieving depression (28,38,45) supports the view that the mechanisms underlying depression are related to those of sleep disturbances. Study of the effects of antidepressants may extend our understanding of the relationship between sleep and depression. Effects on sleep of several antidepressants have been reported. A large majority of the drugs studied increase the concentrations of monoamines by inhibiting the uptake process or monoamine oxidase (MAO) enzymes. However, in addition to changes in monoaminergic transmission, disturbances in second-messenger signaling are also implicated in the pathogenesis of depression (41,44). Alterations in the functions of second-messenger systems are, therefore, possible action sites for antidepressants. Sleep–wake-associated variations in the cyclic adenosine monophosphate (cAMP) concentrations in the preoptic region have been reported (25,26). The aim of our experiments was to study the effects on sleep of an antidepressant, rolipram, which acts on the cAMP system.

Rolipram, 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone, a phosphodiesterase (PDE) inhibitor, is a clinically effective antidepressant (3,9). It increases the availability of cAMP by selectively inhibiting a PDE IV isoenzyme (18,31,37). Unlike conventional antidepressants that inhibit MAO or the reuptake of monoamines, rolipram stimulates both presynaptic and postsynaptic components of the noradrenergic transmission (11,39,43). It enhances the synthesis and the release of noradrenaline (NA). Stimulation of NA synthesis may be due in part to a cAMP-mediated effect on tyrosine hydroxylase. Besides elevating the basal cAMP level, rolipram enhances isoprenaline-induced increases in cAMP concentration (4). Rolipram also influences cytokine synthesis, suppressing the production of several cytokines (34). Rolipram is devoid of anticholinergic effects (30,42).

We studied the effects of chronic rolipram treatment (either 0.1 or 1 mg/kg, twice a day for 11 days) on the sleep–wake activity of rats.

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METHOD

Experimental Animals, Surgery

Male CFY rats were used; the animals weighed 300–350 g at the time of the sleep experiments. Under pentobarbital anesthesia (50 mg/kg), gold-plated screws were implanted over the frontal and parietal cortices and over the cerebellum for EEG recording.

Experimental Conditions, Treatment

The rats were raised in a light:dark cycle of 12 h each (lights on from 0830 to 2030 h), at an ambient temperature of 21°C. The same conditions were maintained in the sound-attenuated experimental chambers. Loud speakers provided low-level continuous noise.

Following the screw implantation operation, the rats lived in individual Plexiglas cages in the experimental chamber. They were allowed 6 to 10 days to recover. Then, to habituate them to the experimental procedure, the rats were connected to light flexible recording cables, and received intraperitoneal (IP) injections of physiological saline twice a day for 6 days. The injections were timed to 10 to 15 min before light onset and dark onset. Treatments before light onset were carried out in a dim light (lasting for 4–6 min). After the period of physiological saline injections, rolipram was administered for 11 days. On day 12, rolipram was withdrawn, and physiological saline was injected again.

The two groups of rats were treated as follows: nine rats received 0.1 mg/kg rolipram (Schering AG, Germany); nine animals were treated with 1 mg/kg rolipram. Rolipram was dissolved in physiological saline, and injected IP in a volume of 0.3–0.4 ml.

In a previous study, it was demonstrated that there were no changes in the sleep–wake activity during a 12-day period in rats injected analogously with physiological saline (15). Accordingly, the chronic administration of physiological saline was not repeated in parallel with rolipram treatment.

Recording, Data Analysis

The sleep–wake activity was recorded for 12 h following the injection at light onset on day 6 of physiological saline administration (baseline day), on days 1, 5, and 11 of rolipram injection, and on day 12 (withdrawal day). The EEG and motor activity (the latter assessed via an electromagnetic transducer activated by cable movements) were recorded on a paper chart (7.5 mm/s). The vigilance states were scored in 40-s intervals, according to the conventional criteria. During wakefulness (W), the rat EEG revealed theta activity; the motor activity record showed continuous, or separated but frequent movements. NREMS was characterized by high-amplitude slow waves and spindles without motor activity. During REMS, highly regular theta activity appeared in the EEG, and small-amplitude deflections were occasionally noted in the motor activity record, indicating twitches. The percentages of the vigilance states were calculated for consecutive 1-h recording periods. Sleep values among the various days were compared by analysis of variance (ANOVA) for repeated measures. ANOVA was performed for the entire 12-h data and for the postinjection first-hour values. The Dunnett test was used for post hoc comparisons. The data for the individual rolipram days were compared with those for the baseline day. p-Values < 0.05 were regarded as statistically significant.

RESULTS

The sleep–wake activity of the animals displayed the usual pattern characteristic of rats, with high percentages of NREMS and REMS in the morning and afternoon, respectively. The 0.1 mg/kg dose of rolipram had no marked effect on sleep. Although ANOVA indicated significant differences in the durations of NREMS, $F(4, 32) = 3.02$, $p < 0.05$, and W, $F(4, 32) = 3.68$, $p < 0.05$, for the 12-h recording periods on the various days, significant differences were not found between the control day and the individual rolipram days. Postinjection hour 1 data on the various days did not differ significantly (ANOVA); only tendencies to a suppression of NREMS and to an enhancement of W were noted after rolipram administration. On day 5 of rolipram treatment, a tendency to a decrease in REMS was observed in postinjection hour 1. [Although post hoc comparison revealed a significant difference, ANOVA indicated only a tendency to alterations in REMS in postinjection hour 1 on the various days ($p < 0.1$).] On the withdrawal day (day 12), NREMS was significantly increased and W was significantly decreased relative to the baseline day, when the data were calculated for the entire 12-h recording period (W, baseline day: 31.7% ± 1.9, withdrawal day: 25.5% ± 0.9; NREMS, baseline day: 56.4% ± 1.9, withdrawal day:

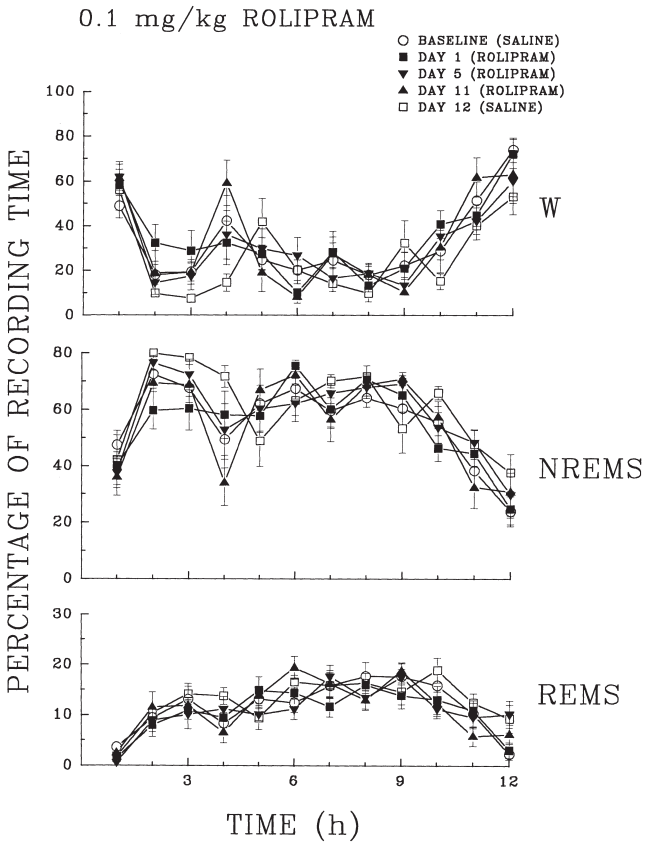

FIG. 1. Effects of 0.1 mg/kg rolipram on the postinjection 12-h sleep–wake activity of rats on the baseline day (saline), on days 1, 5, and 11 of rolipram treatment and on the withdrawal day (day 12, saline). Drugs were administered at the onset of the light period. Patterns of wakefulness (W), non-REM sleep (NREMS), and REM sleep (REMS) are shown during the 12-h light period; mean values ± SE (percentage of recording time) computed for consecutive 1-h periods.

61.6% ± 1.1; percentage of recording time ± SE; Dunnett test, $p < 0.05$; Fig. 1)

The 1 mg/kg dose of rolipram did not induce significant changes in sleep–wake activity relative to the baseline when the data were calculated for the entire 12-h recording periods (ANOVA). Because no significant effect was found for the entire 12-h periods, ANOVA was tested as concerns the first postinjection 1-h periods on the various days, and indicated significant differences in the durations of NREMS, $F(4, 32) = 12.62$, $p < 0.05$, and W, $F(4, 32) = 11.95$, $p < 0.05$. NREMS was suppressed and W was enhanced significantly in postinjection hour 1 on day 1 of rolipram treatment (Dunnett test, $p < 0.05$). These changes in NREMS and W diminished during the chronic treatment and did not reach the level of statistical significance on days 5 and 11. On the withdrawal day (day 12), a tendency to changes in the opposite directions, i.e., a tendency to an increase in NREMS and a decrease in W, was noted in postinjection hour 1. On day 1 of rolipram treatment, a tendency to a decrease in REMS was observed in postinjection hour 2 (Fig. 2).

DISCUSSION

Our results reveal a W-enhancing effect of rolipram, which seems to depend on the dose applied. The high dose (1 mg/kg) of rolipram enhanced W significantly. The observation that one of the side effects of rolipram is insomnia (13) indicates that the drug may enhance W also in humans. Our present results corroborate those of Kawasaki and Takasaki (10), who reported that the administration of rolipram resulted in EEG arousal.

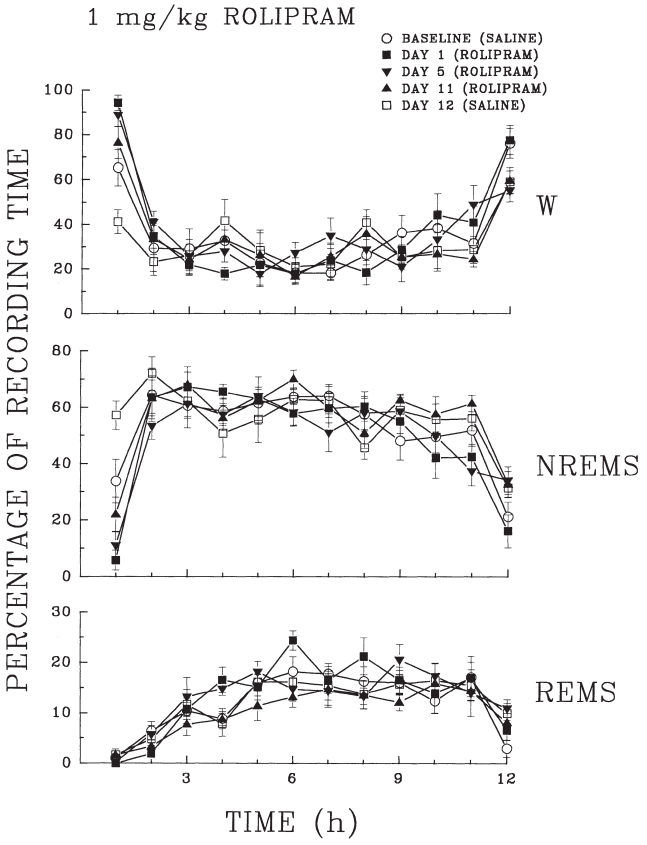

FIG. 2. Effects of 1 mg/kg rolipram on the sleep–wake activity. See legend to Fig. 1.

Rolipram suppresses locomotory and ambulatory activity. Griebel (7) interpreted this observation as behavioral sedation. Our present finding that W is enhanced by a dose (1 mg/kg) of rolipram similar to those (0.39 and 1.56 mg/kg) reported to suppress locomotion (40) does not support the sedative action of the drug.

Rolipram increases the availability of cAMP by a relatively selective inhibition of a PDE isoenzyme (18,31,37). The present findings indicate that stimulation of the cAMP system is accompanied by an increase of W. Drugs that inhibit PDE, for example, caffeine and theophylline, have been reported to enhance W (17,29). The behavioral effects of these drugs, however, are generally attributed to a blockade of the adenosine receptors. In the preoptic region, an area implicated in sleep regulation (2,36), cAMP concentrations exhibit spontaneous oscillations during the sleep–wake cycle, with maximum levels in W (25,26). These findings support the idea that cAMP-mediated processes may be involved in sleep–wake regulation.

Rolipram stimulates both presynaptic and postsynaptic components of NA transmission. Rolipram increases the firing rate of noradrenergic locus coeruleus neurons. Both the synthesis and release of NA are stimulated (partially by cAMP-induced changes in tyrosine hydroxylase activity). In addition, rolipram potentiates the actions of NA at the postsynaptic membrane, due to the inhibition of PDE (11,32,39,43). Despite a stimulatory affect on tyrosine hydroxylase, rolipram does not induce any major changes in dopamine release and metabolism (11). The firing rate of mesolimbic dopaminergic neurons is not enhanced (32). NA transmission contributes to the maintenance of W, at least in part by stimulating α_1 receptors (5,6,35). The effects of rolipram on sleep, may be mediated, at least partially, by the increased release of NA. The overall influence on sleep of the changes in the postsynaptic mechanisms of neurotransmission induced by rolipram is not clear. Stimulation of β_1-adrenergic receptors enhances REMS, whereas administration of β_2 agonists (both kinds of receptors are positively coupled to adenylate cyclase) suppresses REMS (1,8). Increases of cAMP by receptor agonists or antagonists can be accompanied by either an enhancement or a suppression of sleep, for example, dopamine D_1 agonists (D_1 receptors are positively coupled to adenylate cyclase) suppress sleep, whereas D_2 antagonists (D_2 receptors are negatively coupled to adenylate cyclase) enhance sleep (21,22). Rolipram suppresses cytokine production (34). Several of these cytokines, for example, tumor necrosis factor, enhance sleep (23). Suppression of these substances may, therefore, contribute to the enhancement of W by rolipram.

The effects of rolipram on sleep are of short duration: it enhances W only in postinjection hour 1. In the blood plasma, the concentration of rolipram reaches the maximum level 30 min after IV administration, and it declines thereafter (12), but because the half-life of rolipram is 3 h, the pharmacokinetics of the drug cannot really explain the short duration of the effects on sleep. Enhancement of W by stimulation of α_1-adrenoceptors by a moderately high (4 mg/kg) dose of methoxamine is similar to that evoked by rolipram: it is marked, but lasts only for 1 h (24). Tolerance to the awakening effect of the 1 mg/kg dose of rolipram developed during the chronic treatment. This dose, however, is very high compared with those used in clinical practice. After administration of the lower (0.1 mg/kg) dose, only a tendency to an increase in W was noted, but this tendency persisted throughout the chronic treatment. Toler-

ance to the awakening effect cannot be due to a downregulation of α_1-adrenoceptors, because no change in the density of these receptors was reported during chronic rolipram treatment, and the behavioral responses mediated by α_1-adrenoceptors were even potentiated. Diminishing of the enhancement of NA release by rolipram during chronic treatment, however, may contribute to the tolerance, because, in contrast with the effect of the acute administration, no increase in NA utilization was observed after a 2-week treatment with high (1–5 mg/kg) doses of the drug (27).

The effects on sleep of three other antidepressants, all of them reuptake inhibitors, have been studied in an experimental protocol similar to the one used in the present experiment (14,15,20). Amitriptyline, a NA and serotonin uptake inhibitor, trazodone, a serotonin uptake inhibitor, and a small dose (0.1 mg/kg) of nomifensine, a NA and dopamine uptake inhibitor, promoted NREMS. After administration of 5 and 15 mg/kg amitriptyline, the enhancements of NREMS were accompanied by suppressions of REMS. The NREMS-promoting effect was just the opposite of that found after administration of a high (1 mg/kg) dose of nomifensine or rolipram, when W was enhanced. Various effects of antidepressants on sleep have been reported in both animal and human studies, for example, REMS can be suppressed (28) or enhanced (33), and W may be increased (19) or decreased (16). These findings suggest that the effects of antidepressants with various mechanisms of action on sleep may reveal differences, which does not support the existence of a direct, uniform relationship between their antidepressive and sleep-modifying effects.

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