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Adenosine Analogues Modulate the Incidence of Sleep Apneas in Rats

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MONTI, D., D. W. CARLEY AND M. RADULOVACKI. *Adenosine analogues modulate the incidence of sleep apneas in rats.* PHARMACOL BIOCHEM BEHAV **51**(1) 125–131, 1995.—The effects of adenosine A_1 and A_2 agonists on spontaneous central sleep apneas in rats have been examined by simultaneously monitoring sleep and respiration in freely moving unanesthetized animals. Intraperitoneal administration of 1.0 mg/kg of the A_1 receptor agonist $R(-)N^6$-L-(2-phenylisopropyl)adenosine (L-PIA) and 150 and 300 μg/kg of 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamidoadenosine hydrochloride (CGS 21680), a selective A_2 agonist, decreased the apnea index (AI) during sleep. Within a sleep period, AI increased over time in both control and drug-treated animals. For both agonists, doses effective in reducing AI also significantly reduced sleep efficiency.

N^6-Phenylisopropyladenosine (L-PIA) CGS 21680 Sleep apneas Rats Adenosine A_1 receptors Adenosine A_2 receptors Control of respiration Carotid bodies Chemoreceptors

SPONTANEOUS respiratory pauses related to sleep have been reported in unrestrained Sprague–Dawley (24), Fischer (24), and Wistar–Kyoto (30) rats, but the mechanisms underlying these pauses remain unclear. These pauses have been correlated with a loss of diaphragmatic activation (30) and have therefore been referred to as central apneas. Despite the lack of information regarding the mechanisms involved in sleep-related central apneas in man, it has been amply documented that the carotid bodies play a significant role in the peripheral regulation of ventilation during sleep (15,16,27). Indeed, acute exposure to high-altitude or sea-level hypoxia, two well-known carotid body stimuli, are associated with sleep-related apnea (3,17). In addition, mathematical modelling has shown that changes in carotid body responses can affect the incidence of apneas (4,14).

One of the agents that may be relevant for the chemoreceptor activation in the carotid bodies is adenosine, which neuromodulatory actions in both peripheral and central nervous systems have been related to the control of respiration. Pharmacological stimulation of adenosine receptors in the carotid bodies has been reported to stimulate respiration in cats (22,23) and humans (1,20,34,35). The aim of the present study was to test the hypothesis that carotid body stimulation by adenosine A_1 and A_2 receptor agonists would affect sleep-related apneic events in Sprague–Dawley rats.

METHOD

A total of 26 adult Sprague–Dawley rats (350–550 g) were anesthetized with a mixture of ketamine (80 mg/kg) and acetylpromazine (2 mg/kg) administered by intramuscular injection. This was followed by surgical incision of the scalp, bilateral implantation of stainless steel screws into the frontal and parietal bones of the skull for electroencephalographic (EEG) recording, and bilateral implantation of wire electrodes into the dorsal nuchal muscles for electromyographic (EMG) recording (29). All EEG and EMG electrode leads were soldered to a miniature connector plug and fixed to the skull with dental cement. Following the implantation of EEG and EMG electrodes, the wound was closed with sutures.

Respiration was recorded by placing each rat, unrestrained, inside a single-chamber body plethysmograph (PLYUN1R/U; Buxco Electronics, Sharon, CT; dimensions 6″W × 10″L × 6″H) ventilated with a flow of fresh room air at a rate of 2 l/min. Bioelectric activity from the head was carried through a cable plugged onto the animal's connector and passed

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TABLE 1

L-PIA EFFECTS ON APNEA INDEX (APNEAS/h) DURING SLEEP STAGES IN RATS

Sleep Stage	Time Interval	Baseline	L-PIA (mg/kg) 0.3	1.0	1.5
NSW	0–6	5.7 ± 1.2	4.3 ± 0.8	2.2 ± 0.7*	4.5 ± 1.2
SWS	0–6	11.3 ± 2.2	7.7 ± 1.2	4.2 ± 1.7	4.5 ± 1.2
REM	0–6	9.6 ± 3.8	14.5 ± 5.2	19.2 ± 14.5	18.6 ± 9.1

*All values reported are means ± SEM. n = 16 (repeated-measures protocol).
Significantly different from baseline, $p < 0.05$.

through a sealed port to the polygraph. Both respiration and sleep-wake activies were recorded simultaneously on a Grass Model 79D polygraph at a paper speed of 5 mm/s. Polygraphic recordings of sleep and wake were assesed using bifrontal and fronto-occipital EEG and nuchal EMG signals as guidelines on single 60-s epochs.

After 7–10 days' recovery from surgery, each animal was habituated for 16 h to the recording device (respiratory chamber and cable). Throughout the study, all animals were maintained in a fixed environment at 20°C, with 40% humidity, and with the light period from 0800 to 2000 h and the dark period from 2000 to 0800 h. Polygraphic recordings were made from 1000 to 1600 h and the administration of the vehicle or adenosine agonists was done at 0945 h.

Rats were divided in two groups of study: the first group of 16 animals was treated on separate days with the vehicle, 0.3, 1.0, and 1.5 mg/kg of the adenosine A_1 receptor agonist L-PIA; the second group of 10 rats received the vehicle, 3, 30, 150, and 300 μg/kg of CGS 21680, an adenosine A_2 receptor agonist. Prior to recording, rats were treated by intraperitoneal injection with either vehicle or one of the assigned drugs. L-PIA was dissolved in saline whereas CGS 21680 hydrochloride was dissolved in a solution of 20% dimethyl sulfoxide and 80% saline; in all cases, concentrations were adjusted for bolus injection of 1 ml/kg. Solvents for each agonist served as the appropriate vehicle for their respective study group. The studies were all of repeated-measure design; each animal received all treatments assigned in random order and separated by at least 3 days.

Polygraphic recordings were assessed by 1-min epochs. Wakefulness (W) was defined as a high-frequency, low-amplitude EEG with concomitant high EMG tone. Non-slow wave (NSW) was defined by the appearance of spindles and less than 50% high-amplitude, low-frequency EEG delta slow waves, whereas slow-wave sleep (SWS) was defined as having 50% or more delta slow waves. Rapid eye movement sleep (REM) was characterized by a high-frequency, low-amplitude EEG and an absence of EMG tone.

Sleep efficiency was measured for each study as percentage of total epochs staged as sleep (NSW min + SWS min + REM min /360 × 100).

Sleep apneas, defined as cessation of respiratory effort for at least 2.5 s, were scored for each recording session and were associated with the stage in which they occurred: W, NSW, SWS, and REM sleep. Apnea indexes (AI), defined as apneas per hour of each sleep stage, were computed for each state of consciousness (wake, NSW, SWS, and REM) for every study. The duration requirement of 2.5 s was arbitrarily chosen following analysis of pilot data from seven rats not included in the present study. The mean interbreath interval over all sleep stages was 0.8 ± 0.23 (SD) s; 2.5 s thus represents approximately 2 "missed" breaths. Previous investigators have employed a duration criterion of 2 s (24,29). The events detected represent central apneas, because decreased ventilation associated with obstructed or occluded airways would generate an increased plethysmographic signal, rather than a pause (8).

The specific effects of A_1 and A_2 agonists on the apnea index were assesed by analyzing data pooled from the total recording time, and separately from each third of the total recording time. One-way analysis of variance (ANOVA) was employed to evaluate dose- and time-dependent effects of drugs on apnea indexes and sleep architecture. Interaction effects were evaluated using multi-way ANOVA. Multiple comparisons between means were evaluated using the Scheffé F-test, Fisher PLSD, and Dunnett t-test.

RESULTS

Drug Effects on Sleep Apneas

Effects of L-PIA. Overall apnea index showed a trend toward a decrease at L-PIA doses of 0.3 and 1.0 mg/kg in comparison to baseline, although only the 1.0-mg/kg dose

TABLE 2

CGS 21680 EFFECTS ON APNEA INDEX (APNEAS/h) DURING SLEEP STAGES IN RATS

Sleep State	Time Interval	Baseline	CGS 21680 (μg/kg) 3	30	150	300
NSW	0–6	8.9 ± 1.6	10.3 ± 2.0	10.3 ± 1.9	5.3 ± 0.8	4.7 ± 1.3*
SWS	0–6	16.5 ± 7.7	17.7 ± 3.6	18.5 ± 0.9	5.0 ± 2.1	5.6 ± 2.6
REM	0–6	14.9 ± 4.2	25.2 ± 7.6	19.4 ± 3.8	19.4 ± 4.7	18.1 ± 5.6

All values reported are means ± SEM. n = 10 (repeated measures protocol).
Significantly different from baseline, *$p < 0.05$.

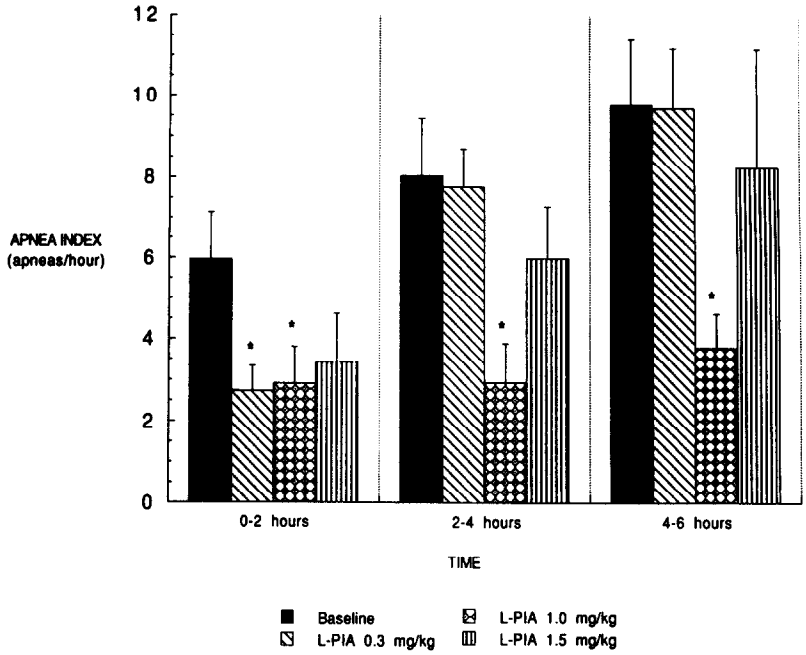

FIG. 1. Apnea indexes by 2-h recording intervals for baseline (vehicle) and 0.3, 1.0, and 1.5 mg/kg of L-PIA (*$p < 0.05$ related to baseline condition of the same interval). Only the 1.0-mg/kg dose maintains a low index compared to baseline across time.

reached statistical significance ($p < 0.05$). The main suppressant effect on AI was observed during NSW sleep ($p < 0.05$) (Table 1).

Effects of CGS 21680. Only the highest doses of CGS 21680 (150 and 300 μg/kg) decreased the apnea index. The 300-μg/kg dose reduced the index to two-thirds of the baseline value ($p < 0.05$). Doses of 3 and 30 μg/kg evoked a nonsignificant ($p > 0.05$) trend toward an increased apnea index. As in the case of L-PIA, the main effect on AI was observed during NSW sleep (Table 2).

L-PIA time-dependent effects on AI. Figure 1 demonstrates the significant decrease in AI after administration of L-PIA, which occurred within the first 2 h following administration of the drug. Although the 0.3- and 1.0-mg/kg doses evoked equivalent significant reductions in AI during the first 2 h, only the effect of the 1.0-mg/kg dose persisted throughout the entire recording period.

In all conditions there was a trend toward increased AI across time, except for 1.0 mg/kg of L-PIA (Fig. 1).

CGS 21680 time-dependent effects on AI. The same increasing trend in the AI reported above for L-PIA was observed after the administration of CGS 21680. Only the two highest doses tended to keep the amount of apneas lower throughout the recording period and only the 300-μg/kg dose had a statistically significant effect ($p < 0.05$) (Fig. 2).

Time course of sleep apnea index. Due to the consistent tendency for AI to increase during the sleep period, which was independent of the drug treatment, the data obtained from all conditions were pooled ($n = 114$) for each 2-h interval, and one-way ANOVA using interval number as a repeated measure was performed.

Figure 3 shows a clear increase in AI with time when all treatments are pooled. The increase in AI with each successive 2-h interval was statistically significant ($p < 0.05$ for each), with overall AI increasing 300%, on average, during the sleep period.

Effects of L-PIA and CGS 21680 on Sleep

L-PIA. Sleep efficiency was not affected by the administration of 0.3 and 1.5 mg/kg of L-PIA ($p > 0.05$). However, there was a significant suppression of total sleep time after the administration of 1.0 mg/kg L-PIA compared to baseline ($p < 0.05$) (Fig. 4). REM sleep time was decreased more by the 1.0- and 1.5-mg/kg doses than was non-REM sleep time (Table 3).

CGS 21680. As shown in Fig. 5, both 150- and 300-μg/kg doses elicited significant reductions in sleep efficiency in relation to baseline. This reduction resulted primarily from a decrease in non-REM, mainly SWS (Table 3).

DISCUSSION

The present study confirms the hypothesis that intraperitoneal bolus injections of both A_1 and A_2 adenosine agonists reduce the incidence of apneas during sleep in the rat. This effect showed a significant dose dependence for both agonists. The greatest L-PIA effect (1.0 mg/kg) reduced AI to less than one-third of the baseline value, whereas the highest (300 μg/kg) dose of A_2 agonist reduced AI to two-thirds of the control value.

Previous reports showed a dose-dependent increase in minute ventilation after intracarotid (IC) administration of adenosine and its analogues in rats (25) and in cats (23). In addition, dose-related increases in chemoreceptor activity were recorded from peripheral ends of sectioned carotid nerves in cats after IC injections of A_2 agonists (21). The present results are consistent with the hypothesis that both A_1 and A_2 agonists may suppress apneic events by stimulating carotid body chemoreceptors.

In relation to central apneas, it has been postulated that either a loss of overall respiratory drive [cf. (6,26)] or an excessive peripheral chemoreceptor drive leading to unstable respiration may be the cause of central apneas (3,14,18,19,31).

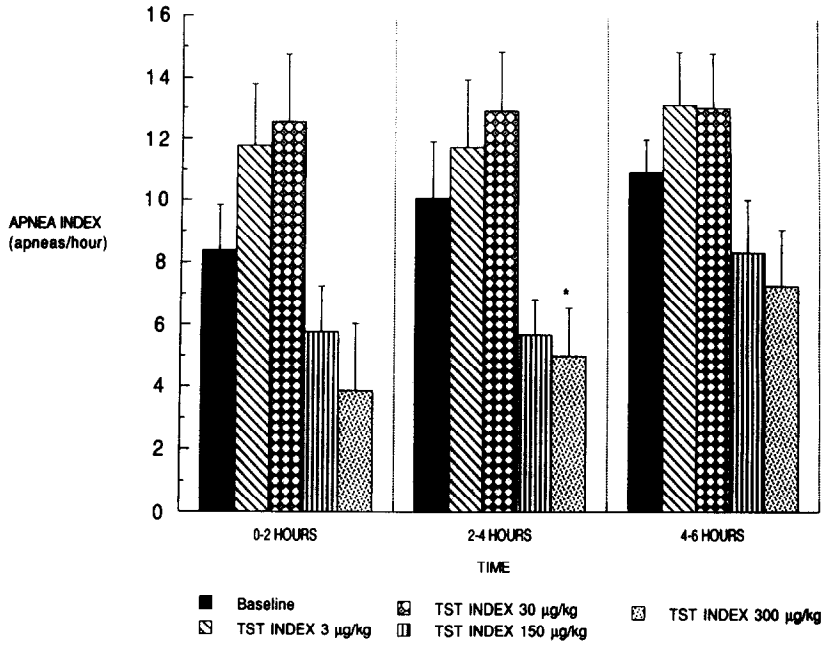

FIG. 2. Apnea indexes for baseline and 3, 30, 150, and 300 μg/kg of CGS 21680 by 2-h intervals; 300 μg/kg is associated with a lower than baseline apnea index in each interval. *$p < 0.05$.

Our results are more consistent with the first postulate (i.e., that apneas in adult rats ensue from a loss of respiratory drive without unstable feedback control). The peripheral stimulant effect elicited by the adenosine agonists in our study would thus act to provide a tonic increase in respiratory drive that may, at least partially, offset the expression of apneas.

The lack of effect on apneas at low doses of each of the drugs used could result from a relative lack of primary effect at carotid bodies (insufficient receptor binding). Perhaps even higher doses of CGS 21680 than those presently employed would have been associated with greater receptor binding, and greater suppression of apneas. In contrast, the highest dose of

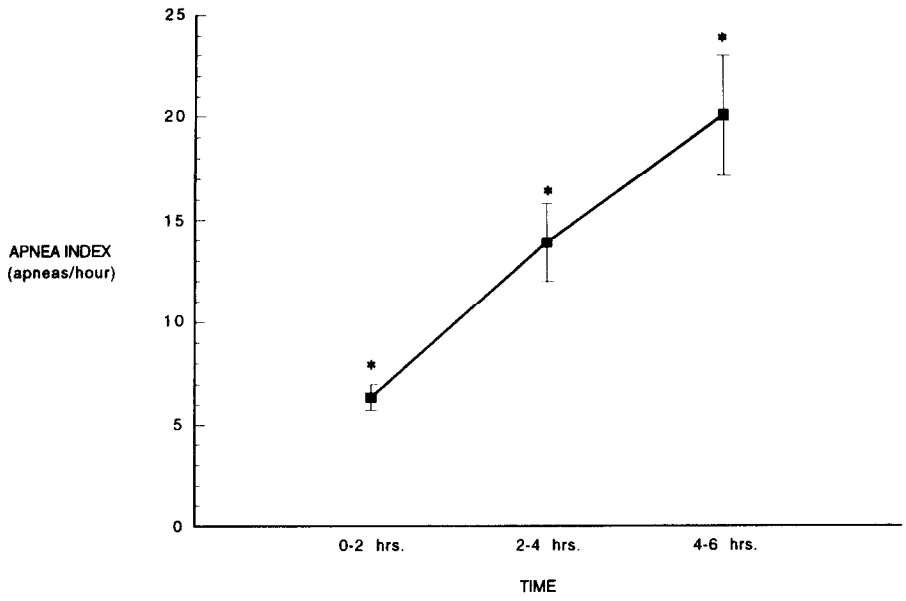

FIG. 3. Temporal structure of apnea index during 6-h recording periods [$N = 114$; pooled data from all conditions (vehicle and agonists) of 26 rats]. *Significant increase ($p < 0.05$, repeated-measures ANOVA and Fisher's PLSD) with respect to preceding 2-h interval.

TABLE 3

EFFECTS OF L-PIA ON SLEEP STAGE PERCENTAGE IN THE RAT

		L-PIA (mg/kg)		
Sleep Stage	Baseline*	0.3*	1.0*	1.5*
NSW (%)	59.3 ± 3.7	55.6 ± 4.2	64.8 ± 5.2	59.9 ± 4.8
SWS (%)	27.4 ± 3.6	33.1 ± 4.0	31.9 ± 4.7	35.1 ± 4.3
REM (%)	13.3 ± 1.3	11.4 ± 1.3	3.3 ± 1.4†	5.0 ± 1.3†

EFFECTS OF CGS 21680 ON SLEEP STAGE PERCENTAGE IN THE RAT

		CGS 21680 (mg/kg)			
Sleep Stage	Baseline	3‡	30‡	150‡	300‡
NSW (%)	42.1 ± 2.3	43.7 ± 3.0	43.6 ± 2.8	38.6 ± 2.3	30.8 ± 3.9†
SWS (%)	12.1 ± 3.0	7.5 ± 2.5	7.9 ± 2.4	2.7 ± 0.8†	6.9 ± 2.5
REM (%)	8.6 ± 1.8	9.4 ± 1.9	11.4 ± 1.7	6.5 ± 1.7	5.2 ± 1.2

All values reported are means of sleep stage efficiency (as percentage of total recording time) during 6-h recording ± SEM.

*n = 16 (repeated-measures protocol).

Significantly different from baseline, †$p < 0.05$.

‡n = 10 (repeated measures-protocol).

L-PIA showed a loss of effect on AI. At this dose, as previously reported (11,36), L-PIA has a general depressant effect on the central nervous system due to possible penetration of the blood–brain barrier. Any central depression of respiratory drive at the highest dose of L-PIA may have offset or reversed the effects of carotid body stimulation on apnea incidence. In combination with central depression of respiratory drive, saturation of an A_1 peripheral effect may have further contributed to the loss of effect on AI at the highest L-PIA dose.

Other effects of peripheral administration of adenosine agonists should also be taken into consideration. Hypotension and hypothermia have been reported with adenosine and adenosine agonists [cf. (7,13,33)] and may have affected our observations. A decrease in core body temperature has potentially significant effects on respiratory chemoregulation, but the influence of hypothermia on sleep apnea, per se, remains unclear. Likewise, to our knowledge, there is no evidence clearly indicating an increase in sleep apneas in hypotensive conditions, although some investigators showed synchronous

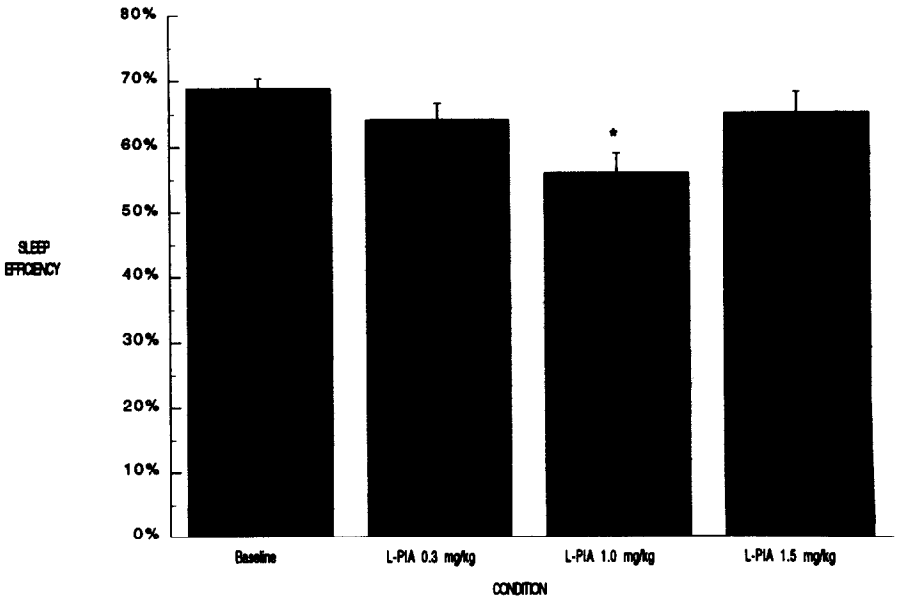

FIG. 4. Effects of L-PIA on sleep efficiency (NSW min + SWS min + REM min/360 × 100) during the 6-h recording period; 1.0 mg/kg of L-PIA decreased the amount of sleep ($p < 0.05$).

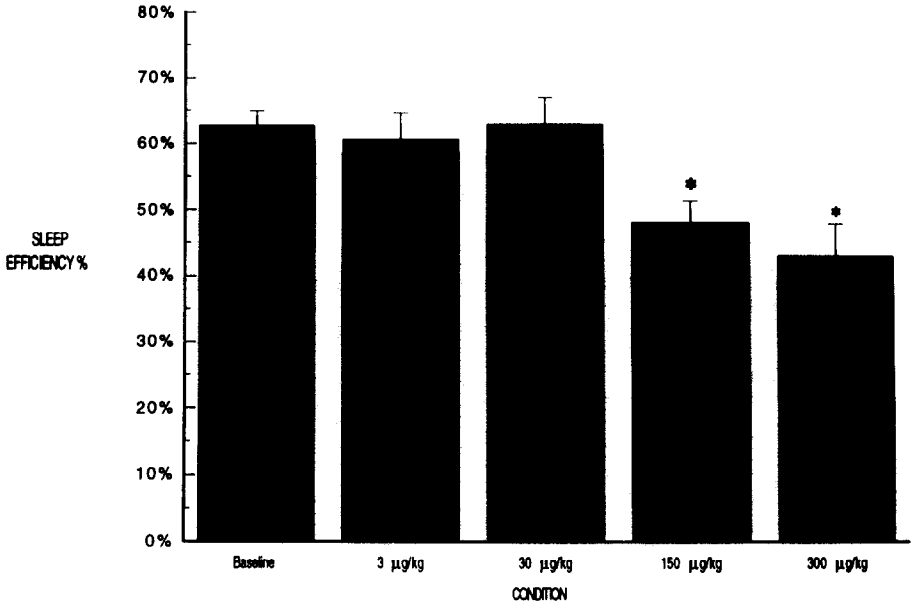

FIG. 5. Effects of CGS 21680 on sleep efficiency (non-REM + REM/360 × 100) during the 6-h recording period. Both 150 and 300 μg/kg reduced the amount of sleep during the recording period ($p < 0.05$).

oscillations in systemic blood pressure and breathing in cats (28). The predominant suppressant effects of both adenosine compounds on sleep apneas during non-REM stages without a similar effect during REM sleep suggest the possibility of different mechanisms leading to apnea in these two states.

Time-Dependent Effects

As demonstrated above, AI exhibited a consistent increase over time during a recording session under all conditions. Although mechanisms responsible for this phenomenon cannot be deduced from the present data, changes in sleep drive, arousal thresholds, core temperature, and other factors may be related to it. Future studies using specific adenosine antagonists may determine whether the present observations depend solely on adenosinergic effects or involve secondary processes related to inhibition of release of monoaminergic neurotransmitters by adenosine (9). It is interesting to note that preliminary studies of clonidine (an α_2 agonist) administration yielded similar effects on AI (5).

Effects on Sleep

As shown in a previous study (29), L-PIA, at the studied doses, was responsible for a decrease in total sleep time at the expense of both non-REM and REM sleep. However, the loss in sleep did not follow any dose-dependent pattern. In the present study, sleep was markedly disrupted exclusively at the 1.0-mg/kg dose of the A_1 agonist. Similar to the L-PIA effect, CGS 21680 at 150- and 300-μg/kg doses also decreased total sleep time at the expense of non-REM and REM sleep. Whether the effect on sleep of these adenosine analogues is related to their effect on central structures that regulate sleep is not clear, because similar effects can be obtained in rats with adenosine antagonists like caffeine (37) or other xanthines (32).

Adenosine agonists may also affect sleep indirectly by causing hypotension and hypothermia. For example, acute hypotension was reported to evoke an arousal response in newborn lambs (12), and hypothermia has been documented as a disruptive factor in sleep continuity (10). In addition, it has also been demonstrated that stimulation of carotid bodies or vagal fibers in dogs can be a potent source of arousals (2).

We conclude from our data that adenosine A_1 and A_2 analogues are able to modulate the amount of apneas during sleep in the rat. Because this effect can be linked to previous reports showing that adenosine stimulates the carotid body chemoreceptors, we interpret this modulation of sleep apneas as a result of peripheral chemoreceptor stimulation by these agents. We have also observed a direct correlation between the effects of these agents on sleep apneas and sleep efficiency. Furthermore, our study has documented an increase in apnea index across time during the sleep period that persists even after administration of A_1 and A_2 agonists.

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