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Sleep Suppressant Action of Quipazine: Relation to Central Serotonergic Stimulation

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FORNAL, C. AND M. RADULOVACKI. *Sleep suppressant action of quipazine: Relation to central serotonergic stimulation.* PHARMAC. BIOCHEM. BEHAV. 15(6) 937–944, 1981.—Administration of quipazine maleate (1–10 mg/kg, IP), a proposed 5-hydroxytryptamine (5-HT) receptor stimulant to rats produced a dose-related suppression of both slow-wave sleep (SWS) and rapid-eye-movement sleep (REMS) accompanied by an increase in head-shaking behavior. These effects were observed during the first 6 hr of a 12-hr EEG recording session. The latencies to the sleep states were markedly prolonged and correlated with the duration of head-shaking behavior induced by the drug. A significant inverse relationship was found between the amount of SWS or REMS and the number of head-shakes occurring during the first 6-hr period. Since head-shaking behavior in rodents has been proposed as a quantitative, behavioral model of central 5-HT activation, the data suggest a causal relationship between enhanced 5-HT activity and sleep suppression. This assumption is further supported by the observation that pretreatment with metergoline (2.5 mg/kg, IP) a 5-HT receptor blocker, reduced quipazine's effects on both SWS and head-shaking behavior.

Quipazine Sleep Head-shaking Increased serotonergic activity

BASED on the 5-hydroxytryptamine (5-HT) sleep hypothesis [20] it has been rationalized that tryptophan, a precursor to 5-HT, may have sedative properties. Indeed, several studies have demonstrated that tryptophan reduces sleep latency in man [13, 14, 25] and in the rat [15]. It has also been reported that administration of tryptophan to humans increased total slow-wave sleep (SWS) time [13, 14, 34], and it was suggested that the action of tryptophan on sleep might be due to an increased level of 5-HT in the brain [14,25]. The increase in 5-HT would then presumably act to facilitate serotonergic neurotransmission.

Recently, our laboratory undertook neurochemical and behavioral studies with tryptophan in rats to determine a possible correlation between changes in the serotonergic system and sleeping behavior [33]. The results indicated that following tryptophan injection, a reduction in sleep latency was obtained which coincided with an elevation of 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of 5-HT, in various brain areas. Although 5-HIAA concentrations were found to be elevated, it was not certain whether this 5-HIAA originated from 5-HT which had already interacted with postsynaptic receptors or from non-functional 5-HT which was metabolized without ever being released [11]. In support of the latter, a recent study using an *in vivo* electrochemical technique failed to detect an increase in extraneuronal concentrations of 5-HT in the rat brain after tryptophan administration [22]. Also, electrophysiological data from rats show that the activity of 5-HT-containing neurons is dramatically depressed in response to systemic injections of tryptophan at doses which elevate brain 5-HT [10,31].

These observations, taken together, suggest that the 5-HT which is synthesized following tryptophan administration is not released from nerve terminals and thus, does not subserve a neurotransmitter role. Since tryptophan's ability to alter brain serotonergic function depends on presynaptic events involving the synthesis, release and metabolism of 5-HT, we focused our attention on the action at the postsynaptic receptor site. We, therefore, undertook experiments to assess the effects of enhanced serotonergic activity on sleep through direct stimulation of 5-HT receptors using quipazine, a 5-HT receptor stimulant [12]. In addition, the effects of quipazine on headshaking activity were examined since recent reports indicate that activation of central 5-HT receptors induces this behavior in rats [4,23]. Furthermore, in order to determine the specificity of the quipazine-induced changes in behavior we used metergoline, a 5-HT receptor blocker [7,9] in an attempt to antagonize the effects of quipazine.

METHOD

Implantation of Electrodes and Polygraphic Recordings

Thirty-seven male Sprague-Dawley rats weighing 300–450

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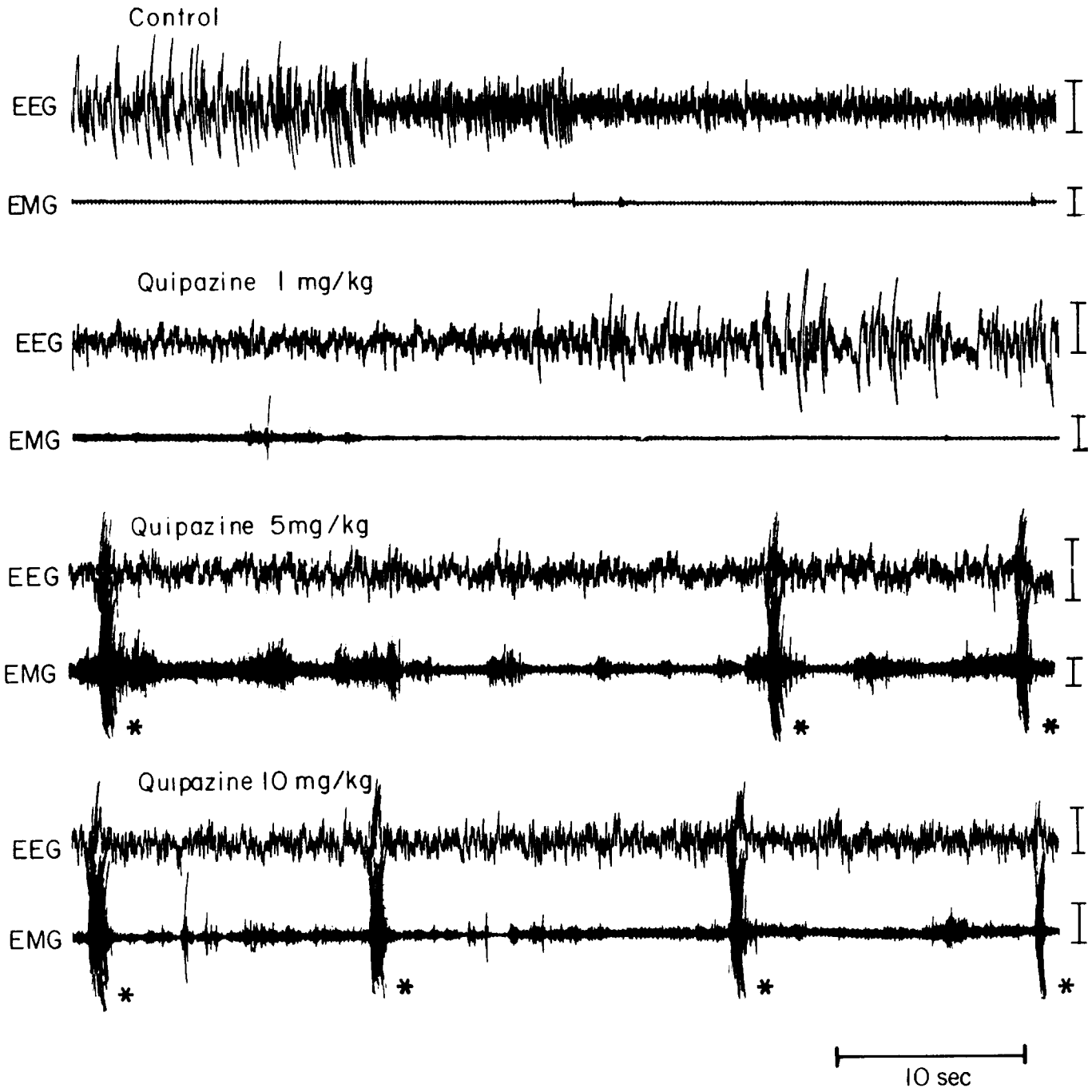

FIG. 1. EEG and EMG recordings of control and quipazine-treated animals obtained 60–80 min after drug administration. Control: transition from SWS to REMS. Quipazine 1 mg/kg: transition from W to SWS. Quipazine 5 and 10 mg/kg: asterisks denote head-shake artifacts during W. Vertical calibration bars: EEG=200 μV; EMG=400 μV.

g were used in these experiments. Each rat was anesthetized with sodium pentobarbital (40 mg/kg, IP), supplemented with ether as required. Atropine methyl nitrate (2 mg/kg, SC) was also given to prevent bronchial congestion. For recording the cortical electroencephalogram (EEG), stainless steel electrodes were screwed bilaterally into the skull over the parietal cortices, and for recording the electromyogram (EMG), stainless steel flexible wire electrodes were implanted in the dorsal neck musculature. The wires of the electrodes were soldered to the appropriate leads of a connector fixed to the skull by dental cement. Two additional stainless steel screws (size 0–80$\times$1/8 inch) were threaded into the skull, one into the occipital bone and the other into the frontal bone, to help secure the implant. After surgery, each

animal was maintained in a separate cage under lighting conditions which consisted of a timer-regulated light period from 8:00 a.m. to 8:00 p.m. All animals were housed in the same room and had free access to food and water for the duration of the study. The experiments were carried out at least one week after surgery.

On the day of the experiment, each animal in its cage was placed under a beam from which a series of mercury slip-ring commutators with a cable connector were suspended down into the middle of the cage. An additional 8-inch high Plexiglas frame was attached over the animal's cage to prevent the rat from escaping during the recording. This arrangement allowed each animal to be recorded in its own cage with relatively free movement. All animals were attached to a dummy cable system for an adaptation period two days before the sleep evaluation. Sleep was monitored by continuous polygraphic recording for 12 hr during the light period. After all injections were made, the animals were left undisturbed for the rest of the recording session. The behavior of the animals was intermittently observed via closed-circuit television.

Recordings were made by a Grass Polygraph Model 79D located outside the recording room, using a chart speed of 5 mm/sec. The half-amplitude frequency response was 1–35 Hz for the EEG and 30–90 Hz for the EMG. The sensitivity of the amplifier was adjusted for each animal at the beginning of the experiment to obtain the most readable tracing.

Drugs and Treatment Regimens

The compounds used in these studies were quipazine maleate (Miles Laboratories, Elkhart, IN) and metergoline (Farmitalia, Milan, Italy). Quipazine was dissolved in 0.9% w/v sodium chloride solution while metergoline was dissolved in propylene glycol. Both drugs were injected intraperitoneally in a final volume of 1 ml/kg. All drug solutions were prepared daily at the beginning of each experimental session. In Experiment 1, the effects of quipazine on behavior were examined. In this study, treated animals received quipazine at doses of 1, 5 or 10 mg/kg at 8:00 a.m.; controls received the same volume of vehicle. In Experiment 2, the effects of metergoline pretreatment on the quipazine-induced changes in behavior were examined. In this study, animals were pretreated with 2.5 mg/kg metergoline or vehicle at 7:00 a.m. One hour later, half of the animals of each pretreatment group received quipazine at a dose of 5 mg/kg while the other half received the drug vehicle. At least four days elapsed between successive injections, and no animal was recorded more than 3 times.

Assessment of Polygraphic Recordings

The polygraphic recordings were evaluated by assigning the predominant electrographic activity of each 30-sec epoch to either wakefulness (W), SWS, or rapid-eye-movement sleep (REMS), according to conventional criteria. The amount of time spent in these three states during the first and second 6 hr periods are presented in minutes. SWS and REMS latencies (the time between the injection and the appearance of the first two minutes of SWS or the first one-minute of REMS episode) were determined as well.

The occurrence of head-shaking was determined by observing the polygraphic correlate of this behavior. Head-shaking produced wide sweeps of the ink pen in the EMG tracings which were frequently so intense as to momentarily disrupt the ongoing recording of EEG activity. These deflections were readily distinguishable from other movement artifacts by their high amplitude, biphasic nature and short time course (about 1 sec). The number of artifacts, i.e., head-shakes, was counted during successive one-hour intervals for each animal over the entire experimental session, and the number of head-shakes occurring during the first and second 6 hr, was determined. Figure 1 illustrates these artifacts in quipazine-treated animals (lower two EMG tracings) as well as EEG and EMG recordings during W, SWS and REMS.

TABLE 1

EFFECTS OF QUIPAZINE ON SLEEP LATENCIES IN RATS

	SWS Latency	REMS Latency
Control	53 ± 5	69 ± 7
Quipazine 1 mg/kg	75 ± 10	118 ± 16*
Quipazine 5 mg/kg	187 ± 21†	234 ± 15†
Quipazine 10 mg/kg	211 ± 23†	309 ± 51†

Results are means ± SEM (min) for 8 animals in each group. All statistical comparisons are made with respect to control.
*$p<0.05$, †$p<0.01$ by Steel's nonparametric statistics [30].

Analysis of Data

When appropriate, statistical comparisons were made by use of one-way analysis of variance (ANOVA) with multiple comparisons performed by the Scheffé Test. In those instances in which Bartlett's Test gave a significant chi-square value for group variances, either Steel's nonparametric test [30] or a nonparametric test based on Kruskal-Wallis Rank Sums [17] was performed. Significance was set at the 0.025 level for the sleep and head-shake data obtained for the 0–6 and 6–12 hr intervals to adjust for multiple testing within the total experimental session. Otherwise, significance was taken at the 0.05 level. Linear regression analysis by the least-squares method was used to assess the relationships between sleep and head-shakes. All mean variations are represented as standard errors.

RESULTS

Experiment 1. Quipazine and Behavior

Effect of quipazine on sleep latencies in rats. Table 1 shows the effect of 1, 5 and 10 mg/kg of quipazine on the latencies to the first SWS and REMS episodes. It can be seen that administration of this drug at doses considered to act preferentially on serotonergic mechanisms produced a dose-related increase in the latencies to these sleep states. The effect on SWS latency was significant for only the 5 and 10 mg/kg doses of the drug. On the average, it took animals approximately 3.5 to 4 times as long to fall asleep following administration of these doses of quipazine as compared to controls. REM sleep latency was significantly increased by all doses of quipazine. While administration of 1 mg/kg of quipazine increased REMS latency by 49 min, 5 and 10 mg/kg doses of the drug delayed the onset of REMS by 3–4 hrs.

TABLE 2

EFFECTS OF QUIPAZINE ON SLEEP AND WAKING IN RATS

	0–6 hr			6–12 hr		
	W	SWS	REMS	W	SWS	REMS
Control	104 ± 8	217 ± 8	41 ± 2	93 ± 9	218 ± 7	48 ± 8
Quipazine 1 mg/kg	118 ± 11	208 ± 8	34 ± 5	97 ± 8	215 ± 5	48 ± 4
Quipazine 5 mg/kg	228 ± 16*	118 ± 14*	14 ± 2†	94 ± 10	217 ± 5	50 ± 6
Quipazine 10 mg/kg	239 ± 16*	113 ± 14*	8 ± 2†	106 ± 9	214 ± 5	39 ± 6

Results are means ± SEM (min) for 8 animals in each group. All statistical comparisons are made with respect to control.

*$p<0.005$, by one-way ANOVA with multiple comparisons performed by Scheffé Test; †$p<0.01$, by Steel's nonparametric statistics [30].

Effects of quipazine on sleep and waking in rats. Table 2 shows the effects of quipazine on the amount of time the animals spent in either W, SWS or REMS during the first and second 6 hr of the recording session. It can be seen that administration of this agent significantly altered sleep and waking time only during the first 6 hr following drug injection. SWS and REMS were significantly reduced by the 5 and 10 mg/kg doses of the drug. The response was almost maximal for the 5 mg/kg dose of quipazine; this dose reduced SWS by 46% and REMS by 66% as compared to controls. Thus, it appears that the drug affected REMS more than SWS. As a result of reduced SWS and REMS, W was increased by 116%.

Effect of quipazine on head-shakes in rats. In agreement with previous findings [6, 16, 23], systemic administration of quipazine produced rapid head-shaking in rats. Figure 2 (left panel) shows the time course for the occurrence of head-shaking following injection of different doses of quipazine. As can be seen, a limited amount of this behavior was present in control animals, usually in association with grooming. After the administration of quipazine, however, head-shaking activity was dramatically increased; this effect was apparent within a few minutes after injection. The animals appeared to exhibit no conscious control over the intermittent shaking of their heads and resumed their normal activities, such as grooming or exploration, between each display of this behavior. The head-shakes consisted of a rapid, rotational movement of the head, neck and shoulders lasting about one sec. Moreover, the frequency and duration of this response varied with the dose of quipazine administered. A small increase in head-shaking activity was observed during the first hr after the administration of a 1 mg/kg dose of quipazine. In contrast, 5 or 10 mg/kg doses of the drug precipitously increased the number of head-shakes during this period of time. The increased incidence of head-shaking observed with these doses of quipazine during the first hr virtually ceased over the next 2–3 hr. It is of interest that the termination of this behavior closely coincided with the appearance of sleep (Table 1). Furthermore, as shown in Fig. 2 (right panel), the response was dose-related when the number of head-shakes was summed for the 6-hr period. The effect reached significance for the 5 and 10 mg/kg doses of quipazine. These doses of the drug increased the number of head-shakes from 37±8 in the control group to 202±37 in the 5 mg/kg group, and to 270±31 in the 10 mg/kg dose group.

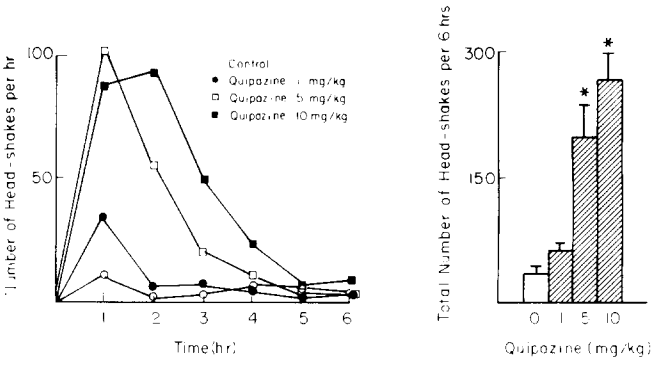

FIG. 2. Effect of quipazine on head-shakes in rats. Left panel shows the time course of the mean number of head-shakes per hr induced by various doses of quipazine as determined by polygraphic recording. Right panel shows histograms of the total number of head-shakes (means±SEM) for each dosage during the 6-hr period. n=8 animals per group. *$p<0.01$ with respect to control by Steel's nonparametric statistics [30].

No difference in the number of head-shakes was observed during the second 6-hr period. At this time, controls had 40±6 head-shakes, and animals receiving the 1, 5 or 10 mg/kg doses of quipazine had 38±11, 37±11, 33±7 head-shakes, respectively (data not shown). The rates of head-shaking observed here for control and quipazine-treated animals are somewhat greater than those reported in previous studies using only behavioral observations [6, 16, 23]. These differences may be attributed to the presence of the recording cable attached to the animal's head which served as a stimulus to promote head-shaking in our study. Since head-shaking in rodents may be due to increased activity of 5-HT neurons [4, 21, 23], these data suggest that the doses of quipazine used here were effective in stimulating the central serotonergic system.

Correlation between changes in SWS or REMS and the number of head-shakes induced by quipazine. To determine whether a relationship existed between changes in sleep and

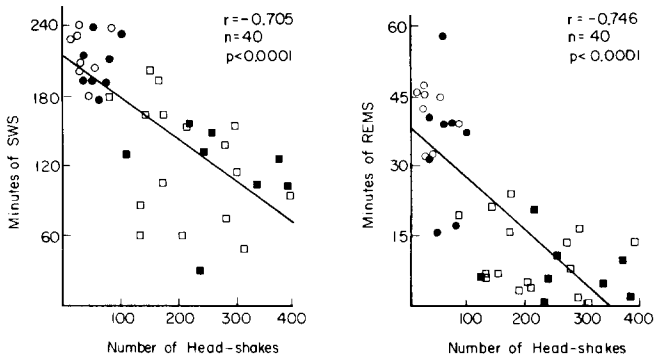

FIG. 3. Correlation between the amount of SWS (left panel) or REMS (right panel) and the number of head-shakes during the first 6 hrs after quipazine administration. Data pairs were compared using linear regression by the least-squares method. ○ Control (n=8), ● Quipazine 1 mg/kg (n=8), □ Quipazine 5 mg/kg (n=16), ■ Quipazine 10 mg/kg (n=8).

the frequency of head-shaking induced by different doses of quipazine, the amount of SWS or REMS was plotted against the number of head-shakes during the first 6-hr period for each animal. Additionally, 8 animals that had received 5 mg/kg of quipazine during Experiment 2 were also included. Both of these groups showed similar responses to quipazine. The data from all animals were then subjected to linear regression analyses.

As shown in Fig. 3 (left panel), a highly significant inverse correlation ($r=-0.705$, $p<0.0001$) was found between the amount of SWS and the number of head-shakes elicited by quipazine during this time period. A similar correlation ($r=-0.746$, $p<0.0001$) was also observed for REMS. However, this latter observation may be related to the suppression of SWS with quipazine since some SWS usually precedes the appearance of REMS.

TABLE 3

EFFECTS OF METERGOLINE PRETREATMENT ON THE QUIPAZINE-INDUCED CHANGES OF SLEEP LATENCIES IN RATS

	SWS Latency	REMS Latency
Control	56 ± 15	109 ± 24
Metergoline 2.5 mg/kg	79 ± 14	216 ± 17*
Quipazine 5 mg/kg	205 ± 24†	300 ± 21†
Metergoline 2.5 mg/kg + Quipazine 5 mg/kg	92 ± 13‡	233 ± 21*

Results are means ± SEM (min) for 8 animals in each group.
*$p<0.025$, †$p<0.0005$ with respect to control, ‡$p<0.001$ with respect to quipazine; by one-way ANOVA with multiple comparisons performed by Scheffé Test.

Experiment 2. Antagonism of Quipazine-Induced Behavioral Effects by Metergoline

In order to determine whether the effects of quipazine on sleep are mediated via activation of serotonergic receptors, animals were studied with and without pretreatment with metergoline (2.5 mg/kg), a selective blocker of 5-HT receptors. For this study, 5 mg/kg of quipazine was selected since this dose significantly altered sleep latencies and sleep states.

Effect of metergoline pretreatment on the quipazine-induced changes of sleep latencies. As shown in Table 3, pretreament with metergoline 1 hr before the administration of quipazine, reduced quipazine's prolongation of SWS la-

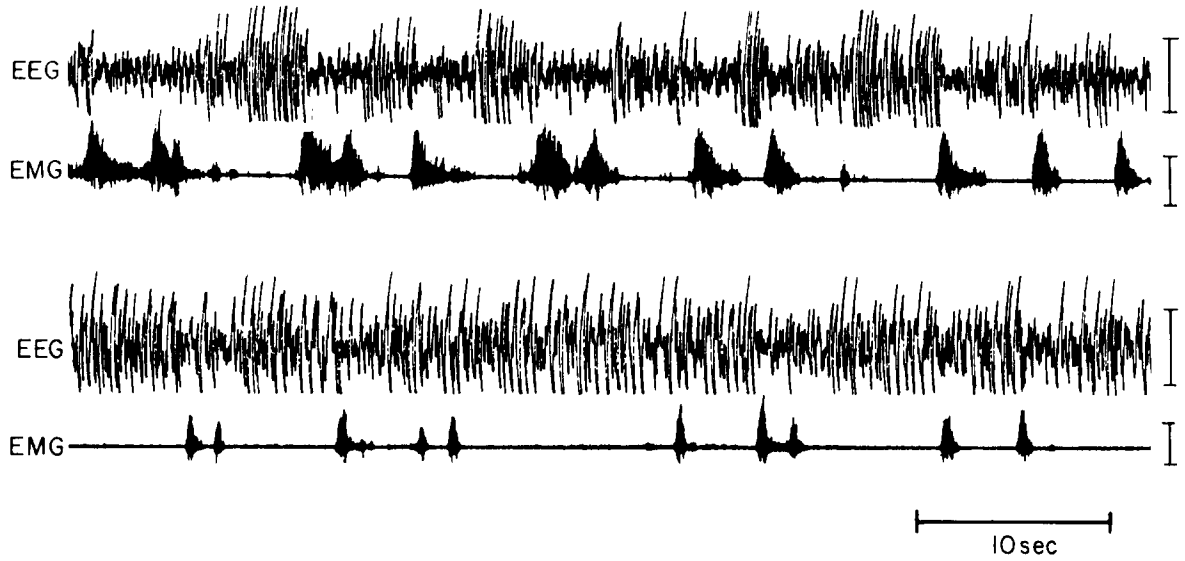

FIG. 4. EEG and EMG recordings of a metergoline (2.5 mg/kg IP) treated animal. Note the numerous bursts of EMG activity which coincided with periods of EEG desynchronization (upper tracings). The same EMG activity but of a lesser intensity was also observed during sleep (lower tracings). Vertical calibration bars: EEG=200 μV; EMG=400 μV.

TABLE 4

EFFECTS OF METERGOLINE PRETREATMENT ON THE QUIPAZINE-INDUCED CHANGES OF SLEEP AND WAKING IN RATS

	0–6 hr			6–12 hr		
	W	SWS	REMS	W	SWS	REMS
Control	115 ± 14	212 ± 10	33 ± 5	107 ± 7	202 ± 5	50 ± 4
Metergoline 2.5 mg/kg	135 ± 7	208 ± 6	17 ± 3*	98 ± 5	209 ± 4	54 ± 5
Quipazine 5 mg/kg	226 ± 21†	123 ± 20†	6 ± 3*	89 ± 11	225 ± 11	46 ± 4
Metergoline 2.5 mg/kg + Quipazine 5 mg/kg	130 ± 8‡	214 ± 7‡	16 ± 2*	83 ± 9	224 ± 11	52 ± 3

Results are means ± SEM (min) for 8 animals in each group.

*$p<0.025$ with respect to control by one-way ANOVA with multiple comparisons performed by Scheffé Test.

†$p<0.01$ with respect to control, ‡$p<0.025$ with respect to quipazine; by multiple comparisons nonparametric statistics.

tency to levels not significantly different from controls. However, administration of metergoline alone did not affect SWS latency. These findings suggest that the delay in SWS onset seen with quipazine may be due to the action of the drug on 5-HT receptors. In contrast, pretreatment with metergoline failed to prevent the effect of quipazine on REMS latency. In fact, metergoline alone significantly delayed the onset of REMS. Therefore, the ability of both quipazine and metergoline to delay REMS onset suggests that these effects may not involve serotonergic mechanisms.

Effect of metergoline pretreatment on the quipazine-induced changes in the sleep-wakefulness cycle. As shown in Table 4, metergoline pretreatment effectively prevented the suppression of SWS and increased W seen with quipazine during the first 6 hr of EEG recording. However, metergoline pretreatment did not appreciably alter the action of quipazine on REMS since administration of metergoline alone suppressed REMS. Although the total amount of SWS was unchanged by metergoline, sleep was disturbed in some animals, as revealed by frequent bursts in electromyographic activity. This phenomenon was readily distinguishable from the head-shake artifacts observed in the EMG tracings by its lower amplitude (<0.5 mV), monophasic nature and frequently longer time course (≥2 sec). As shown in Fig. 4 (upper tracing), this behavior interfered with the onset of sleep and also was observed during sleep (lower tracing). Varying degrees of this activity were detected in about half of the animals receiving metergoline. In some animals, the characteristic electromyographic activity lasted for as long as 4 hr and was present also in those animals receiving quipazine following metergoline pretreatment.

Effect of metergoline pretreatment on the quipazine-induced change of head-shaking in rats. Figure 5 shows the effect of metergoline pretreatment on the quipazine induced head-shaking response. At the dose used, metergoline completely prevented the increased incidence of head-shaking normally seen with quipazine injection at the beginning of the recording session. The time course of this antagonism as well as the total number of head-shakes over the 6-hr period for the different treatment groups are shown in the left and right panels, respectively. As can be seen, the quipazine group had 244±40 head-shakes during the 6-hr period compared to the control group, which had 37±5. Metergoline pretreatment totally prevented the quipazine-induced head-shaking and reduced the occurrence of this behavior to levels below that observed in controls. Animals receiving the combination of the two drugs had 19±5 head-shakes. Metergoline alone also reduced this behavior below control levels showing 7±2 head-shakes for this period of time. Thus, the head-shaking phenomenon produced by quipazine appears to be dependent upon the activation of 5-HT receptors, since metergoline completely blocked this response. These data further confirm the observations that metergoline is an effective antagonist of 5-HT-mediated head-shaking [23].

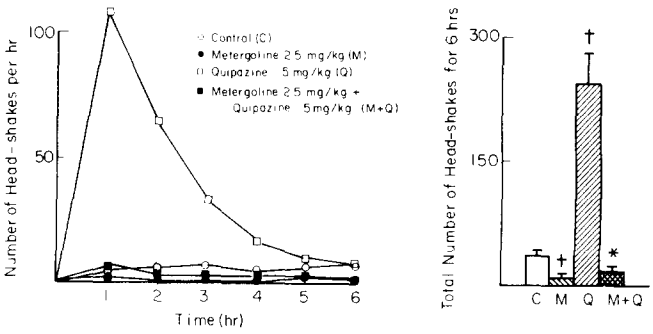

FIG. 5. Effects of metergoline pretreatment on the quipazine-induced head-shakes in rats. Left panel shows the time course of the mean number of head-shakes per hr after various drug treatments as determined by polygraphic recording. Right panel shows histograms of the total number of head-shakes (mean±SEM) for each group during the 6-hr period. n=8 animals per group. *$p<0.05$, †$p<0.01$ with respect to control by Steel's nonparametric statistics [30].

DISCUSSION

Using systemic administration of relatively low to moderate doses of quipazine as a means to preferentially stimulate 5-HT receptors, the present study investigated the effects of enhanced 5-HT activity on sleep. Our findings, presented in Tables 1 and 2, show that the administration of

quipazine prolonged SWS and REMS onset in a dose-related manner and significantly decreased the length of time animals spent in these sleep states. In agreement with the proposed stimulatory action of quipazine on 5-HT [12], our data, presented in Tables 3 and 4, show that the effects of quipazine on SWS were reduced by pretreatment of rats with a 5-HT receptor blocker, metergoline. This indicates that the suppression of SWS by quipazine may have been due to the direct action of the drug on 5-HT receptors.

However, the mechanism by which quipazine affects REMS is less clear. Administration of quipazine produced a dose-related reduction of REMS, but this effect could not be prevented by metergoline pretreatment. This lack of antagonism may be related to the finding that metergoline pretreatment alone suppressed REMS, as previously reported [8]. On the other hand, the response may not involve a 5-HT mechanism and thus would not be blocked by the antagonist.

As evidence for increased 5-HT activity, Fig. 2 shows that administration of quipazine produced a dose-related increase in the number of head-shakes during the first 6 hr of polygraphic recording. The duration of the head-shaking behavior was coincident with the onset of sleep. Moreover, the frequency of head-shaking was inversely related to the length of time the animals spent sleeping during this period (Fig. 3). Given that head-shaking is a quantitative sign of central 5-HT receptor stimulation [4,23], these data further suggest a relationship between enhanced 5-HT activity and sleep suppression. The simultaneous blockade of quipazine-induced head-shaking (Fig. 5) and decrease in SWS by pretreatment with metergoline can be taken as strong evidence in support of such a relationship.

It could be argued, however, that the sleep suppression induced by quipazine may be only indirectly mediated via the production of head-shaking behavior which interferes with sleep. While it is true that quipazine-treated animals only fell asleep after head-shaking ceased, several observations suggest that this behavior is not directly related to the inhibition of sleep. As evidence for this, during the period of head-shaking there were many intervals of 2–10 min duration free of head-shakes, yet sleep continued to be totally inhibited by quipazine. Also, there were no episodes of cortical synchronization during these intervals between successive head-shakes which would have indicated attempts by the animals to initiate sleep. Furthermore, once sleep had occurred the amplitude of the EEG was reduced and gradually increased until well developed, high-voltage slow-waves were observed in the EEG. These observations led us to conclude that the effects of quipazine on sleep are not due to the production of head-shakes but rather to an action of the drug on sleep *per se*. In contrast, we have presented polygraphic evidence which clearly indicates that the abrupt bursts in EMG activity produced by metergoline disrupt sleep. Not only did this activity interfere with the sleep onset, it also coincided with brief periods of EEG desynchronization during SWS.

In addition to head-shaking, a complex behavioral syndrome characterized by tremor, rigidity, forepaw treading, Straubs tail, hindlimb abduction and lateral head-weaving has been observed in rats after treatments which increase 5-HT activity [19]. However, these behavioral responses are elicited at higher doses of 5-HT agonists than those necessary to produce the head-shaking phenomenon [4], and thus represent potent stimulation of 5-HT receptors. The simultaneous display of these behaviors would obviously interfere with sleep. In this respect, large doses of quipazine (25 or 50 mg/kg), which have been reported to induce the behavioral syndrome [4,12], were not used here. Instead, we used comparatively small doses of the drug which were found to cause head-shaking behavior in animals. Subsequently, this response was then used as a behavioral index for the assessment of central 5-HT activity.

Although the action of quipazine on sleep has not been previously examined in rodents, the effects of the drug have been characterized in cats. Systemic administration of quipazine caused EEG synchronization in cats as well as behavioral alterations characterized primarily by catatonic, stereotyped postures, lack of responsiveness to external stimuli and sham-rage reactions. These effects, similar to those observed after the injection of the immediate 5-HT precursor, 5-hydroxytryptophan, were antagonized by cinanserin, a 5-HT receptor blocker [29]. In contrast to these behavioral responses, the same authors reported that local application of microcrystals of either quipazine or 5-HT to the pontine raphe nuclei accelerated sleep onset and significantly prolonged total sleeping time [29].

Since the discharge rate of midbrain 5-HT neurons is markedly depressed with microiontophoretic application of various 5-HT agonists [1,10], chemical stimulation in these latter experiments also would be expected to produce an inhibition of raphe activity. The decrease in raphe neuronal discharge would thus lead to a reduction in 5-HT release at post-synaptic receptor sites in the brain. This is of interest since recent electrophysiological and biochemical studies have revealed that the discharge rate of raphe neurons [24,32] and the release of endogenous 5-HT [27] are significantly diminished during sleep relative to wakefulness. On the other hand, electrical stimulation of the midbrain raphe region would be expected to increase 5-HT activity in the brain as indicated by the accompanying increase in 5-HIAA [2,28] and decrease in 5-HT in the forebrain [2]. This procedure, however, does not induce behavioral sleep in laboratory animals [3, 18, 28] and in some studies has resulted in mild arousal [18,26]. In contrast, cooling of the raphe has been reported to induce SWS and REMS [5].

At this point, we wish to emphasize that these data should not be taken as evidence to indicate that the serotonergic system is involved in the inhibition of sleep in physiologic conditions. Instead, they indicate that pharmacological stimulation of certain types of 5-HT neurons in the brain reduces sleep time.

In conclusion, our data provide general support for a causal relationship between quipazine stimulation of central 5-HT receptors and the sleep suppressant action of the drug.

ACKNOWLEDGEMENT

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