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Serotonin Receptor Activation in Rats Previously Deprived of REM Sleep[1]

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SANTOS, R. AND E. A. CARLINI. *Serotonin receptor activation in rats previously deprived of REM sleep.* PHARMACOL BIOCHEM BEHAV 18(4) 501–507, 1983.—The effects of serotonin precursors (L-5-hydroxytryptophan and L-tryptophan, with or without MAO inhibitors) and of agonists (quipazine and 5-methoxy-N,N-dimethyltryptamine-MeO-DMT) were studied in 3 day REM-deprived or control rats, by recording the presence of the serotonin syndrome and the number of head shakes. The REM sleep-deprived rats showed a larger incidence of the serotonin syndrome and a greater number of head shakes in comparison to the control animals, when challenged with the serotonin precursors. Conversely, REM sleep deprivation did not modify the responsiveness of rats to 0.75–6.0 mg/kg of MeO-DMT and to 2.4–6.0 mg/kg of quipazine. However, REM-deprived rats reacted less than controls to 0.3–1.25 mg/kg of quipazine. Increased turnover due to REM sleep deprivation could explain the augmented responsiveness of the rats to the serotonin precursors. Conversely, the decreased responsiveness to quipazine could result from receptor hyposensitivity due to intense receptor activation, caused by the increased turnover, during the 3 day period of REM sleep deprivation.

REM sleep deprivation Serotonin Quipazine Tryptophan Serotonin agonists
Receptor supersensitivity

RAPID eye movement sleep deprived (REMd) rats respond to the administration of dopaminergic drugs in an exaggerated fashion as compared to control (non deprived) animals. Thus, aggressive behavior elicited by either apomorphine, bromocriptine or piribedil is greater in the REMd rats [6, 16, 21, 22, 26, 27, 31]. Also, stereotyped behavior induced by apomorphine is enhanced by previous REM sleep deprivation [27,31]. Further work showed that the enhancement of responses to the dopamine agonists is not due to presynaptic events as the level and turnover of dopamine are not modified and alpha-methyl-p-tyrosine is not able to abolish or even to decrease it [5,25]. These data lend support to the hypothesis that REM sleep deprivation induces a supersensitivity of dopamine receptors in brain [5, 25, 27]. Supersensitivity of dopamine receptors in brain of laboratory animals can be induced by several procedures such as lesions of dopaminergic pathways, acute or chronic blockade of dopamine receptors, inhibition of dopamine synthesis and depletion of catecholamine stores [2, 7, 11, 24, 28]. As a rule, all these manipulations led the animals to exaggerated behavioral responses to apomorphine, as found in the REMd rats.

Development of receptor supersensitivity by manipulating the dynamics of a given neurotransmitter through specific treatments such as inhibition of synthesis, blockade of receptors or lesions of nerve pathways, is not restricted to dopamine. In fact, supersensitivity of serotonin receptors is also obtained after treatments with the neurotoxin 5,7-dihydroxytryptamine [18, 19, 30], the serotonin antagonists methergoline and methysergide [14,20] and the synthesis inhibitor p-chlorophenylalanine [10].

These data led us to investigate whether REM sleep deprivation would affect serotonergic responses as well. In order to answer this question, precursors and agonists of serotonin were administered to control and REMd rats. The behavioral responses elicited by these drugs, that is, the serotonin syndrome [13,23] and the number of head shakes [3,15], were taken as a measure of serotonin receptor activation and were compared in both groups of animals. During

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the course of development of this work, it was reported [16] that REM sleep deprivation increased the number of head shakes induced by the serotonin agonist quipazine.

METHOD

Animals and REM Sleep Deprivation

Three to four month old male Wistar rats were used. REM sleep deprivation was achieved by introducing the animals in pails containing water at a level 1 cm below the surface of a round platform inside the pail, measuring 6 cm in diameter. Food was available ad lib inside the pail. After 3 days the animals were withdrawn from the pail, injected IP with drug under study and introduced into Plexiglas cages measuring 17×25×30 cm, to facilitate inspection. Control rats were maintained individually for 3 days in their home wire cages measuring 15×20×30 cm. "Wet controls" were rats maintained for 3 days in the pails but the platforms were 14 cm in diameter. These procedures have been routinely used in our laboratories [27].

Drugs

L-5-Hydroxytryptophan—5HTP—(Sigma Labs) was diluted in distilled water containing a small quantity of HCl 0.1 N to facilitate solubilization. In other experiments, 5HTP was suspended in water plus tween-80 (1%) mixture. L-Tryptophan methylester (Sigma Labs) was dissolved in distilled water. Carbidopa (Merck, Sharp and Dohme) and pargyline hydrochloride (Sigma Labs) were solubilized in distilled water. Quipazine maleate (Miles Labs) and 5-methoxy-N,N-dimethyltryptamine-MeO-DMT—(Sigma Labs) were solubilized with HCl 0.1 N and distilled water. All substances were diluted immediately before use. The injections were made via the intraperitoneal route in volumes of 1.0 mg/kg, and the amounts injected are expressed as the salts.

Behavioral Measures

Immediately after the injection of the drug under study the animals were introduced individually into the Plexiglas cages and the presence or absence of the serotonin syndrome as well as the number of head shakes were recorded during the next 20 to 120 min (dependent upon the treatment). The results were recorded every 5-min period up to complete the above mentioned time interval. The syndrome was considered to be present when at least 3 of the following 5 signs were simultaneously present within any of the 5-min periods: forepaw padding, lateral head weaving, head tremor, Straub tail and hindlimb abduction [13,23]. During the same period of observation the number of head shakes was also scored. The shake behavior is a movement similar to the pinna reflex elicited by stimulation of the auditory canal of the rat [3,15].

Experiment 1—Effects of 5HTP Alone or in Combination with Carbidopa

Fifty rats were deprived of REM sleep during 3 days; 50 other animals were maintained individually in their home cages for the same period of time. Five to 10 min after the end of deprivation, REMd and control rats were injected in groups of 10 with 150, 175, 200 and 225 mg/kg of 5HTP; a fifth group of control and REMd rats received the vehicle. Immediately after the injections the number of animals presenting the serotonin syndrome and the number of head shakes presented by each animal were scored for the following 12 periods of 5-min each (60 min). Comparisons between control and REMd groups for each dose of 5HTP were made through the Student's t and Fisher tests, respectively, for the total number of head shakes in 60 min and the percentage of rats with serotonin syndrome.

Another 30 rats were REM deprived for 3 days; 20 control rats were maintained isolated for 3 days in their home cages. Following that all these animals received 25 mg/kg of carbidopa and 30 min later groups of 10 REMd rats received, respectively, control solution, 75 and 150 mg/kg of 5HTP. The 2 groups of 10 control rats each were treated with 75 and 150 mg/kg of the aminoacid. For the next 120 min, at every 5-min period, the presence of the serotonin syndrome and the number of head shakes were recorded. The total number of head shakes presented during the 2-hr period of observation as well as the number at every 5-min interval were considered for comparisons.

In a complementary experiment, 10 3-day REMd rats and 10 "wet control" rats, that is, submitted for 3 days to the large platforms, were treated with 25 mg/kg of carbidopa and 75 mg/kg of 5HTP and as above observed for the following 2 hours, at each 5-min interval.

Experiment 2—Effects of L-Tryptophan in Combination with Pargyline

Forty-six REMd and 40 control rats were employed. All the animals received 50 mg/kg of pargiline followed 60 min later by 50 (16 REMd and 16 controls), 100 (14 and 14) or 150 mg/kg (10 and 10) of L-tryptophan. The remaining 6 REMd rats were injected with the vehicle. Twenty min later, at every 5-min interval up to complete 60 min the number of head shakes and the percentage of animals undergoing the serotonin syndrome were recorded and statistically analysed as above.

Experiment 3—Effects of MeO-DMT and Quipazine

Eighty-two rats were deprived of REM sleep for 3 days; 74 other rats were maintained isolated in their home cages (controls). Groups of 6 to 16 REMd and control rats, depending upon the dosage and the solubilizing agent employed, were injected with control solution, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 mg/kg of MeO-DMT. Solutions for dosages of 1.0, 2.0, 4.0 and 6.0 mg/kg were prepared in Tween-80 and 0.1 N HCl was employed for the other dosages.

Following the injections, the number of head shakes and of rats displaying the serotonin syndrome were recorded for the next 20 min. Statistical analysis were through the Student's t and Fisher tests.

For experiments with quipazine, 113 REMd and 109 controls were employed. Five to 10 min after the end of the 3 day deprivation (REMd) or 3 day isolation in home cages (controls) groups of 6 to 18 animals received either control solution or doses varying from 0.3 to 60 mg/kg of quipazine, as specified in Table 2. For the next 30 min the presence of the serotonin syndrome and the number head shakes were recorded. Statistical analyses were performed as above.

Another 6 REMd rats were allowed to rest 96 hr after the end of the 3 day deprivation period and were then challenged with 10 mg/kg of quipazine and observed for 30 min. Six rats which remained isolated 7 days in their home cages were used as controls.

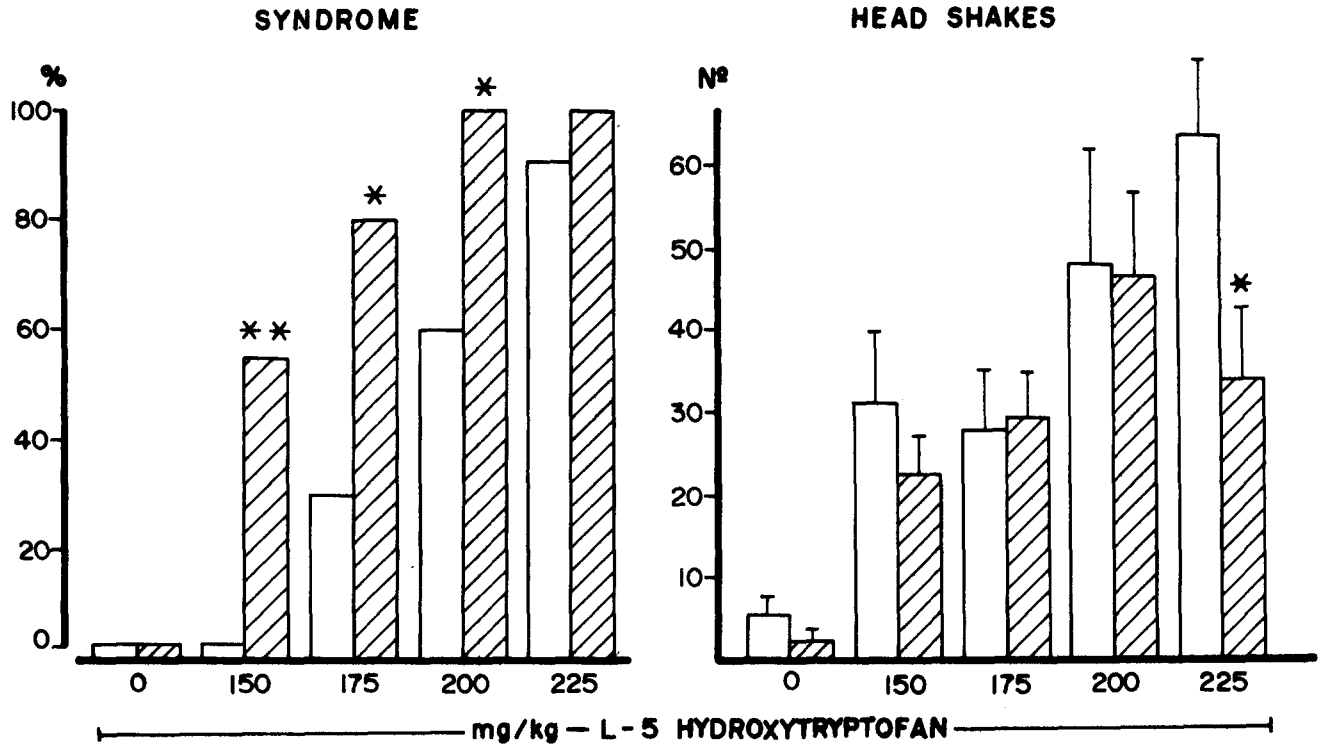

FIG. 1. Left side: Percentage of control (open columns) and REM deprived rats (hatched columns) displaying the serotonin syndrome after treatment with several doses of L-5-hydroxytryptophan. Right side: Mean total number of head shakes emitted by the same animals. The bars above the columns, represent the standard errors of the means. Asterisks indicate statistically significant differences between both groups (*$p \leq 0.05$; **$p \leq 0.01$).

RESULTS

Experiment 1

Figure 1 shows that REMd and control rats treated with the vehicle did not show the serotonin syndrome and displayed only a few head shakes during the 60-min period of observation. Conversely, with 150, 175 and 200 mg/kg of 5HTP a significantly larger percentage of the REMd rats, as compared to the controls, displayed the syndrome. On the other hand, no difference between the two groups of rats was observed concerning the number of head shakes at the dosage range of 150–200 mg/kg. However, control rats with 225 mg/kg displayed significantly larger number of head shakes when compared to the similarly-treated REMd rats.

Pretreatment with 25 mg/kg of carbidopa strongly potentiated both the amount of head shakes and the number of rats displaying the syndrome. This potentiation was particularly noticed in the REMd rats in which both parameters were significantly greater than in controls at the 75 mg/kg dosage of 5HTP (Fig. 2). The number of head shakes induced by the double treatment carbidopa plus 75 mg/kg dosage of 5HTP, measured at every 5-min interval up to 120 min, is shown is Fig. 3. It is seen that beginning at the 20th min REMd rats displayed nearly twice the number of head shakes as controls in all of the following 5-min periods. The right part of Fig. 3 shows that rats maintained for 3 days of the 14 cm platforms located in the pails (wet controls) did not differ from the control animals. That is, the increase of head shakes brought about by carbidopa plus 5HTP in REMd rats is not due to the stress that accompanies the REM deprivation procedure.

Experiment 2

Figure 4 shows that for the 3 doses (50, 100 and 150 mg/kg) of L-tryptophan, the percentage of animals showing the syndrome was greater in the REMd group; however, this difference fell short of statistical significance ($p \leq 0.10$). The number of head shakes was also greater for the REMd rats, with the 50 mg/kg data showing statistical significance ($p \leq 0.05$).

Experiment 3

As seen in Table 1, 0.75–6.0 mg/kg of MeO-DMT diluted in an acid vehicle elicited a small number of head shakes irrespective of whether the animals were REMd or not. Beginning with 1.5 mg/kg the majority of the animals presented the serotonin syndrome and again no differences were noted between control and REMd rats. In other groups of animals MeO-DMT was also administered suspended in a Tween-80-water mixture. Similar results were obtained, that is no differences were noted between both groups of animals.

Quipazine elicited from the control rats amounts of head shakes which increased dose-dependently from 0.3 to 5.0 mg/kg (Table 2). From this last dose up to 60.0 mg/kg the number of head shakes decreased progressively. Concerning the serotonin syndrome, beginning with 10 mg/kg the per-

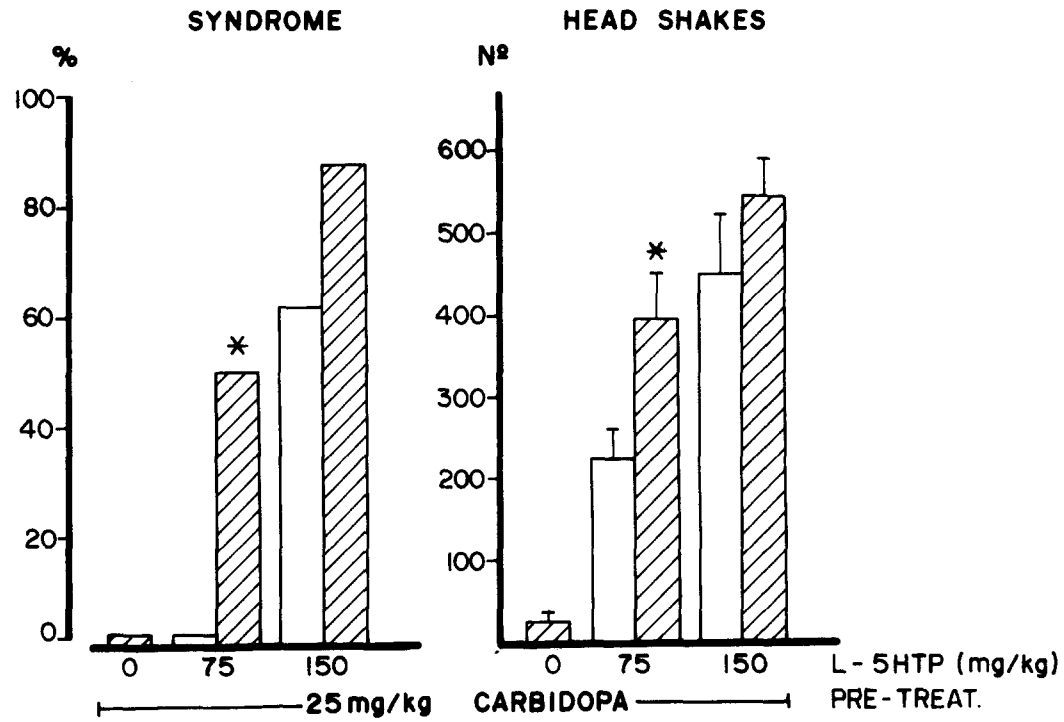

FIG. 2. Serotonin syndrome and head shakes presented by control and REMd rats after pretreatment with 25 mg/kg of carbidopa followed by control solution, 75 or 150 mg/kg of L-5-hydroxytryptophan. To be read as in Fig. 1.

centage of rats showing it increased steadily. That is, it seems that both measured behavior are mutually exclusive, as the increase in one of them was accompanied by the decrease of the other.

Comparisons between both groups of rats showed that the REMd animals emitted significantly less head shakes at the dosages of 0.3, 0.6 and 1.25 mg/kg of quipazine.

Finally, REMd rats which were allowed to rest for 4 days after deprivation did not differ from their respective controls. Thus, these rats showed 14.7±9.6 and 21.0±10.4 head

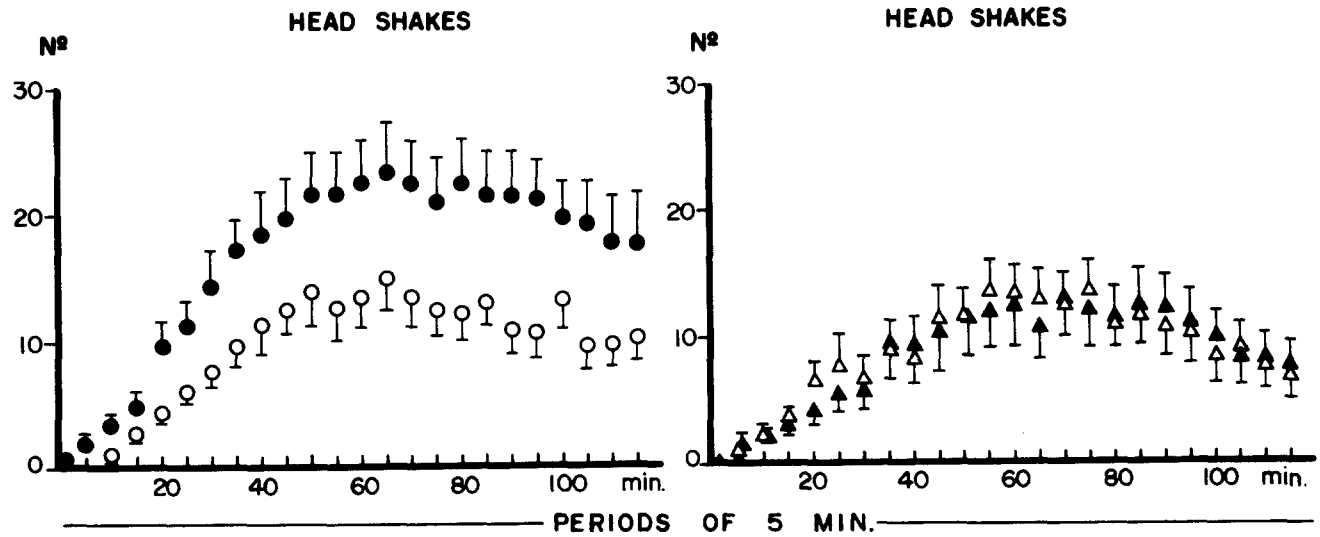

FIG. 3. Left side: Mean number of head shakes, at every 5 min interval during 2 hr, emitted by control (open circles) and REMd (closed circles) rats after receiving 25 mg/kg of carbidopa followed by 75 mg/kg of L-5-hydroxytryptophan. The bars above or below each symbol represent the standard errors of the means. Right side: The same measure performed in other control (open triangle) and in "wet control" (closed triangles) rats, after the same treatment.

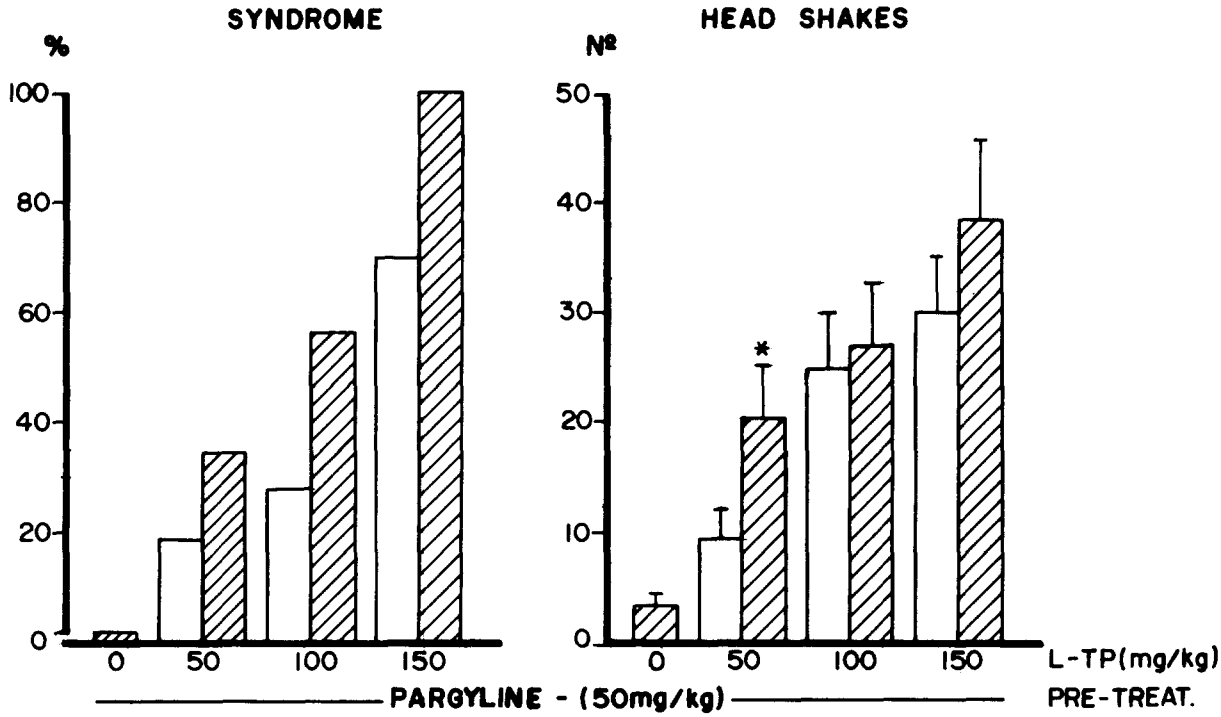

FIG. 4. Serotonin syndrome and head shakes presented by control and REMd rats after pretreatment with 50 mg/kg of pargiline followed by control solution, 50, 100 and 150 mg/kg of L-tryptophan. To be read as in Fig. 1.

TABLE 1

SEROTONIN SYNDROME AND HEAD SHAKES ELICITED BY 5-METHOXY-N,N-DIMETHYLTRYPTAMINE (MeO-DMT), SOLUBILIZED IN 2 SOLVENT SYSTEMS, IN CONTROL AND REM-SLEEP DEPRIVED RATS

MeO-DMT (mg/kg)	Solvent	No. of Animals		Mean (±S.D.) head shakes		% with 5HT syndrome	
		Control	REMd	Control	REMd	Control	REMd
Control Solution	HCl	7	6	3.7 ± 5.1	1.0 ± 1.7	0	0
0.75		6	5	0.8 ± 1.2	2.2 ± 2.3	0	0
1.5		6	7	0.0 ± 0.0	1.0 ± 0.8	83.3	71.4
3.0		6	6	1.0 ± 2.0	1.0 ± 0.2	83.3	100
6.0		4	4	1.0 ± 1.1	0.0 ± 0.0	100	100
1.0	Tween-80	8	11	2.5 ± 5.5	1.7 ± 2.2	0	18.2
2.0		11	16	0.8 ± 1.2	1.6 ± 2.7	27.3	18.7
4.0		13	14	2.7 ± 7.4	1.7 ± 3.8	69.2	71.4
6.0		13	13	2.6 ± 4.9	0.0 ± 0.0	58.8	100

shakes, respectively, and none of them presented the syndrome (data not shown in Table 2), after being challenged by 10 mg/kg of quipazine.

DISCUSSION

L-5-Hydroxytryptophan, at dosage levels of 150, 175 and 200 mg/kg, elicited the serotonin syndrome in a significantly higher percentage of rats which were previously deprived of REM sleep for 3 days when compared to control animals (Fig. 1). However, there was no difference in the number of head shakes emitted by animals of both groups. On the other hand, when the animals were pretreated with carbidopa, REMd animals reacted more to 75 mg/kg of 5HTP, not only by a larger number of head shakes but also by greater percentage of animals showing the serotonin syndrome (Fig. 2). There has been discussions whether the neurochemical and behavior alterations brought about by REM sleep deprivation are due to the deprivation per se, or to the stress that inevitably accompanies the deprivation procedure employed [5]. In order to shed some light on this question, "wet control" rats were challenged with the double treatment carbidopa plus 5HTP. The "wet control" rats displayed equal number of head shakes along 2 hr, as the control animals,

TABLE 2

SEROTONIN SYNDROME AND HEAD SHAKES ELICITED BY QUIPAZINE IN CONTROL AND REM-SLEEP DEPRIVED RATS

Quipazine (mg/kg)	No. of Animals		Mean (±S.D.) head shaks		% with 5HT syndrome	
	Control	REMd	Control	REMd	Control	REMd
Control Solution	12	11	7.2 ± 9.6	7.2 ± 7.3	0	0
0.3	9	9	17.6 ± 13.4	5.1 ± 3.1†	0	0
0.6	9	9	31.0 ± 12.9	4.9 ± 4.4‡	0	0
1.25	18	18	36.1 ± 24.3	21.7 ± 11.8*	0	0
2.5	6	6	40.5 ± 30.1	37.2 ± 16.7	0	0
5.0	10	10	43.3 ± 10.8	42.8 ± 16.6	0	0
10	9	11	15.8 ± 23.4	18.7 ± 11.4	11.1	18.2
15	8	8	27.0 ± 16.3	30.8 ± 26.7	0	12.5
30	7	7	8.6 ± 12.0	12.8 ± 12.4	28.6	28.6
45	8	10	4.1 ± 5.7	7.0 ± 15.6	87.5	70.0
52.5	7	8	11.3 ± 15.3	3.2 ± 3.6	85.7	100.0
60	6	6	4.0 ± 5.8	1.8 ± 1.2	83.3	100.0

Symbols indicate statistically significant differences from controls (*$p \leq 0.05$; †$p \leq 0.02$; ‡$p \leq 0.001$, Student's t-test, two tailed).

and these groups had only half of the head shakes presented by the REMd rats (Fig. 3). Several previous studies demonstrated that rats on small and large platforms are similarly stressed and that animals on small platforms have significantly less REM sleep than the "wet control" rats (for review see [29]).

Another question is whether the effects of 5HTP were really mediated through the synthesis of 5HT in serotonergic neurons, as it can be taken up and decarboxylated by other monoaminergic neurons and the resulting serotonin could alter the functioning of these neurons [1,17]. L-Tryptophan is hydroxylated to 5HTP only within the serotonergic neurons and thus yields serotonin specifically in these neurons. Thus, the increased number of head shakes displayed by the REMd rats after 75 mg/kg of L-tryptophan (Fig. 3) suggests that the hyperresponsiveness to both aminoacids observed after REM sleep deprivation is, in fact, resultant of an alteration in the serotonin neurons. Furthermore, several authors have reported that the increase in head shakes and the presence of the serotonin syndrome occur as an activation of central serotonin receptors resulting from the previous administration of these serotonin precursors [3, 13, 15, 23].

The hyperresponsiveness of the REMd rats to the amino acids could be explained by two mechanisms. It has been reported that REM sleep deprivation increases serotonin turnover in brain, although the REM rebound that follows deprivation might also be playing a role [4, 8, 12]; consequently, more serotonin could be formed from the precursors in the brain of REMd rats explaining their greater responsiveness. An alternative interpretation might be that REM sleep deprivation changes the sensitivity of the postsynaptic serotonergic receptors. In other words, the same hypothesis suggested to explain the hyperresponsiveness of REMd rats to dopaminergic drugs [27], would apply also to the serotonin system.

The results obtained with the two agonists of the serotonin receptors favor the former possibility. MeO-DMT at a dose range of 0.75 to 6.0 mg/kg provoked essentially the same amount of responses irrespective whether the rats were REM deprived or not (Table 1). In order to eliminate the remote possibility that acidification of solution was in some unspecified way altering the results, MeO-DMT was also suspended in Tween-80; as seen in Table 1, the same results were obtained. Quipazine, at doses from 5 to 60 mg/kg also affected similarly both groups of rats. As seen in Table 2, in REMd and control rats, 5 mg/kg induced a maximum of head shakes and no serotonin syndrome; increasing the doses produced progressively more serotonin syndrome and simultaneously decreased the number of head shakes. However, with the dose of 1.25 mg/kg and below a significant difference was noticed between the rats: REMd animals displayed less head shakes in three dosage levels. This finding is not at a contradiction with the interpretation given for the results with the precursors. It may well be that the increased turnover induced by REM sleep deprivation augmented the serotonin availability to the receptors rendering them hyposensitive. Consequently, at low doses quipazine induced less head shakes in the REMd rats. Higher doses reached a plateau effect, masking the differences.

One point deserving further attention concerns with the meaning of the two behavior used to measure serotonin receptors activation. With 5HTP (Fig. 1) REM deprivation potentiated only the number of animals presenting the syndrome; with carbidopa plus 5HTP (Fig. 2) both, the syndrome and the head shakes were equally potentiated by REM deprivation. In REMd rats quipazine decreased only the number of head shakes; neither agonist influenced the amount of serotonin syndrome. We feel that more research should be done in order to clarify whether both behavior are the reflection of activation of different 5HT receptors in brain or even if different neurotransmitters are also playing a role. However, Drust *et al.* [9], after also observing that the occurrence of the syndrome coincided with a decrease in the number of head shakes, suggested that the head shakes probably signal low level 5HT-receptor stimulation, whereas the serotonin syndrome indicates more intense receptor activation.

Finally, our results with quipazine are at contradiction with the findings of Mogilnicka [16]. She found a decrease in head shakes when REMd rats were challenged with 10 mg/kg immediately after the completion of deprivation. However, when the elapsed time was 96 hr the REMd rats displayed more head shakes. As seen in the Table 2 and in the results of Experiment 3, we were not able to confirm this finding.

REFERENCES

1. Aghajanian, G. K. and I. M. Asher. Histochemical fluorescence of raphe neurons: selective enhancement by tryptophan. *Science* **172:** 1159–1161, 1971.
2. Andén, N. E., A. Dahlström, K. Fuxe and K. Larsson. Functional role of the nigro-neostriatal dopamine neurons. *Acta Pharmacol Toxicol* **24:** 263–275, 1966.
3. Bedard, P. and C. J. Pycock. "Wet-dog" shake behavior in the rat: a possible quantitative model of central 5-hydroxytryptamine activity. *Neuropharmacology* **16:** 663–670, 1977.
4. Borbély, A. A., P. Staigrad and I. Tobler. Effect of sleep deprivation on brain serotonin in the rat. *Behav Brain Res* **1:** 205–210, 1980.
5. Carlini, E. A. REM sleep deprivation and dopamine in the CNS. *Rev Pure Appl Pharmacol Sci*, in press.
6. Carlini, E. A. and C. J. Lindsey. Pharmacological manipulations of brain catecholamine and the aggressive behavior induced by marihuana in REM-sleep-deprived rats. *Aggress Behav* **1:** 81–99, 1974.
7. Costentin, J., H. Marçais, P. Protais, M. Baudry, S. de la Baume, P.-P. Martres and J.-C. Schwartz. Rapid development of hypersensitivity of striatal dopamine receptors induced by alpha-methylparatyrosine and its prevention by protein synthesis inhibitors. *Life Sci* **21:** 307–314, 1977.
8. Cramer, H., A. Tagliamonte, P. Tagliamonte, J. Perez-Cruet and G. L. Gessa. Stimulation of brain serotonin turnover by paradoxical sleep deprivation in intact and hypophysectomized rats. *Brain Res* **54:** 372–375, 1973.
9. Drust, E. G., R. S. Sloviter and J. D. Connor. Effect of morphine on "wet-dog" shakes caused by cerebroventricular injection of serotonin. *Pharmacology* **18:** 299–305, 1979.
10. Fleisher, L. N., J. R. Simon and M. H. Aprison. A biochemical-behavioral model for studying serotonergic supersensitivity in brain. *J Neurochem* **32:** 1613–1619, 1979.
11. Gianutsos, G., R. B. Drawbaugh, M. D. Hynes and H. Lal. Behavioral evidence for dopaminergic supersensitivity after chronic haloperidol. *Life Sci* **4:** 887–898, 1974.
12. Hery, F., J.-F. Pujol, M. Lopez, J. Macon and J. Glowinski. Increased synthesis and utilization of serotonin in the central nervous system of the rat during paradoxical sleep deprivation. *Brain Res* **21:** 391–403, 1970.
13. Jacobs, B. L. and H. Klemfuss. Brain stem and spinal cord mediation of a serotonergic behavioral syndrome. *Brain Res* **100:** 450–457, 1975.
14. Klawans, H. L., D. J. D'Amico and B. C. Patel. Behavioral supersensitivity to 5-hydroxytryptophan induced by chronic methysergide pretreatment. *Psychopharmacology (Berlin)* **44:** 297–300, 1975.
15. Matthews, W. D. and C. D. Smith. Pharmacological profile of a model for central serotonin receptor activation. *Life Sci* **26:** 1397–1403, 1980.
16. Mogilnicka, E. REM sleep deprivation changes behavioral response to catecholaminergic and serotonergic receptor activation in rats. *Pharmacol Biochem Behav* **15:** 149–151, 1981.
17. Moir, A. T. B. and D. Eccleston. The effects of precursor loading in the cerebral metabolism of 5-hydroxyindoles. *J Neurochem* **15:** 1093–1108, 1968.
18. Olpe, H.-R., R. Ortmann, B. Fehr and P. C. Waldmeier. Experimentally induced supersensitivity of neocortical neurons to microiontophoretically administered serotonin. *Brain Res* **224:** 367–374, 1981.
19. Ortmann, R., S. Martin and P. C. Waldmeier. Supersensitivity to 1-5-hydroxytryptophan after 5,7-dihydroxytryptamine injections in desmethylimipramine- and nomifensine-pretreated rats: behavioral evidence for postsynaptic supersensitivity. *Psychopharmacology (Berlin)* **74:** 109–114, 1981.
20. Samanin, R., T. Mennini, A. Ferraris, C. Bendotti and F. Borsini. Hyper- and hyposensitivity of central serotonin receptors: [^{3}H]-serotonin binding and functional studies in the rat. *Brain Res* **189:** 449–457, 1980.
21. Serra, G., M. R. Melis, A. Argiolas, F. Fadda and G. L. Gessa. REM sleep deprivation induces subsensitivity of dopamine receptors mediating sedation in rats. *Eur J Pharmacol* **72:** 131–135, 1981.
22. Silva, C. C., F. Campos and E. A. Carlini. Aggressive behavior induced by apomorphine in rats submitted to four stressful situations. *Res Commun Psychol Psychiat Behav* **4:** 353–367, 1980.
23. Sloviter, R. S., E. G. Drust and J. D. Connor. Specificity of a rat behavioral model for serotonin receptor activation. *J Pharmacol Exp Ther* **206:** 339–347, 1978.
24. Tarsy, D. and R. J. Baldessarini. Behavioral supersensitivity to apomorphine following chronic treatment with drugs which interfere with the synaptic function of catecholamines. *Neuropharmacology* **13:** 927–940, 1974.
25. Tufik, S. Increased responsiveness to apomorphine after REM sleep deprivation: supersensitivity of dopamine receptors or increase in dopamine turnover. *J Pharm Pharmacol* **33:** 732–733, 1981.
26. Tufik, S. Changes of response to dopaminergic drugs in rats submitted to REM-sleep deprivation. *Psychopharmacology (Berlin)* **72:** 257–260, 1981.
27. Tufik, S., C. J. Lindsey and E. A. Carlini. Does REM sleep deprivation induce a supersensitivity of dopaminergic receptors in the rat brain? *Pharmacology* **16:** 98–105, 1978.
28. Ungerstedt, U. Postsynaptic supersensitivity after 6-hydroxydopamine-induced degeneration of the nigrostriatal dopamine system. *Acta Physiol Scand* Suppl. **82:** 367–398, 1971.
29. Vogel, G. W. A review of REM sleep deprivation. *Arch Gen Psychiatry* **32:** 749–761, 1975.
30. Wang, R. Y., C. de Montigny, B. I. Gold, R. H. Roth and G. K. Aghajanian. Denervation supersensitivity to serotonin in rat forebrain: single cell studies. *Brain Res* **178:** 479–497, 1979.
31. Zelger, K. D. and E. A. Carlini. The persistence of hyperresponsiveness to apomorphine in rats following REM sleep deprivation and the influence of housing conditions. *Eur J Pharmacol* **80:** 99–104, 1982.