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The effect of venlafaxine on behaviour, body weight and striatal monoamine levels on sleep-deprived female rats

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Abstract

Partial sleep deprivation is clinically associated with fatigue, depressive symptoms and reduced memory. Previously, it has been demonstrated that venlafaxine, an atypical antidepressant, increases the levels of noradrenaline and serotonin in rat hippocampus. The aim of this study was to evaluate the effects of venlafaxine on depression, anxiety, locomotor activity and memory in a model of REM sleep (REMs) deprivation in rats. We have also studied the influence of venlafaxine on monoamine levels in the striatum. Six groups of animals (N=20 each) were treated with saline or venlafaxine (1 or 10 mg/kg) during 10 days, submitted or not to REMs deprivation and studied with the forced swimming test of Porsolt (STP), plus-maze, passive avoidance and open-field tests right after sleep deprivation. Animals were also studied for passive avoidance 24 h later (rebound period). Brain samples for monoamine measurements were collected either immediately after REMs deprivation or after 24 h. Both REMs deprivation and venlafaxine showed an antidepressant effect. An anxiolytic effect was also observed after REMs deprivation. Previous treatment with venlafaxine blocked the antidepressant and anxiolytic effects of REMs deprivation. REMs deprivation alone and treatment with venlafaxine 10 mg/kg increased locomotor activity, and this effect was inhibited by venlafaxine in REMs deprived rats. Both venlafaxine treatment and REMs deprivation induced weight loss. Venlafaxine treatment, but not REMs deprivation, induced an increase in striatal dopamine (DA) levels. The combination of REMs deprivation and venlafaxine treatment was associated with an increase in serotonin turnover 24 h after rebound sleep. In this study, venlafaxine treatment hindered most behavioral effects of REMs deprivation and was associated with an interference on dopamine and serotonin systems in the striatum.

Keywords: Sleep deprivation; Venlafaxine; Depression; Anxiety; Serotonin; Dopamine; Rats

1. Introduction

The association of mood disorders with sleep complaints, insomnia or hypersomnia have long been described (Benca et al., 1992; Nofzinger et al., 1993; Ward et al., 2000). Several chronic illnesses present with depressive symptoms, and currently antidepressants are commonly used. Chronic partial sleep deprivation is a frequent underrecognized public health problem associated with clinical conditions as obstructive sleep apnea syndrome and shift work and commonly manifests with fatigue and depressive symptoms (Cheshire et al., 1992; Kaplan, 1992; Borak et al., 1996; Smith et al., 2002). Mood disorders, sleep changes and secondary disruption of social rhythms further contributes to changes in neurobiological processes, neurotransmitter functions, neuroendocrine regulation and loss of neurophysiological control of sleep–wake cycle (Ehlers et al., 1988; Kasper and Wehr, 1992).

REM sleep (REMs) deprivation has been shown to cause an antidepressant effect and to precipitate mania attacks in patients with bipolar disorder (Kasper and Wehr, 1992;

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Wright, 1993; Barbini et al., 1996). It has also been shown that REMs deprivation interrupts vital biological mechanisms essential to cognitive function and other physical abilities (Koslowski and Babkoff, 1992; Pilcher and Huffcutt, 1996; Leproult et al., 1997). The most visible consequence of REMs deprivation is sleepiness (Bonnet and Arand, 1998). Severe REMs deprivation results in nystagmus, ptosis, hyperreflexia and reduction of pain threshold (Kollar et al., 1968). Experimental studies using REMs deprivation in animals have also shown severe physical changes, such as skin lesions, weight loss, hypothermia and energy expenditure (Bergmann et al., 1989). After REMs deprivation (72–96 h), animals stay awake for approximately 30 min, and during this period, hyperactivity, irritability, aggressiveness and hipersexuality are observed (Gessa et al., 1995).

Substances that interfere with dopamine (DA) and serotonin have been studied in association with REMs deprivation. Neuroleptics, lithium and naloxone reduce sleep latency after REMs deprivation (Fadda et al., 1993; Gessa et al., 1995). Imipramine and desipramine have been shown to increase the antidepressive effect of REMs deprivation in the forced swimming test of Porsolt (STP; Asakura et al., 1993). Venlafaxine, an atypical antidepressant, is a strong inhibitor of serotonin and noradrenaline re-uptake and a moderate inhibitor of dopamine re-uptake (Ellingrod and Perry, 1994; Rockville, 1994). It has been recently reported that venlafaxine treatment increases the levels of noradrenaline and serotonin in rat hippocampus (Piacentini et al., 2003) and results in higher neocortical concentration of serotonin and noradrenaline, lower 5-hydroxyindole-3-acetic acid levels and increased locomotor activity (Wikell et al., 2001). In rodents, increased active behaviors, such as climbing and swimming, after venlafaxine treatment may reflect enhanced 5-hydroxytryptamine (5-HT) and dopamine activity (Reneric and Lucki, 1998).

The aim of this study was to evaluate the effects of venlafaxine, an atypical antidepressant with serotonergic, noradrenergic and low dopaminergic action, in the STP, plus-maze, passive avoidance, open-field test, and body weight in REMs deprived rats. We have also studied the influence of venlafaxine treatment on striatal monoamines levels.

2. Material and methods

2.1. Animals

Female Wistar rats, 3 months old and weighing 150–200 g, were used throughout the study. Rats were housed (two animals per cage) at controlled temperature (24–25 °C) and were exposed to a 12/12-h light–dark cycle, with food and water ad lib. Animals were kept at the same room, and we assumed that as ovarian-cycle synchrony is mediated by environmental pheromones, estrous cycle variation was not a major concern. The study has been approved by the Ethics Committee for Animal Research at the Department of Physiology and Pharmacology, Federal University of Ceara, Brazil.

2.2. Drug

Venlafaxine Hydrochloride (EFEXOR XR, Wyeth-Whitehall, Brazil), 75 mg, was dissolved in distilled water and administered orally, 1 and 10 mg/kg at same times around 12:00 p.m.

2.3. REM sleep deprivation technique

The instrumental methods used to induce REMs deprivation are usually based in the single-platform method developed by Jouvet et al. (1964) for cats and adapted for rats. Van Hulzen and Coenem (1981) introduced the multiple platform method using several platforms into a large water tank reducing movement restriction stress induced by the single-platform technique. In the present study, the multiple-platform method was further modified. Five platforms (5 cm in diameter) placed into a tank (40×30 cm) filled with water until 1 cm of the upper surface of the platforms were used. In each tank, two rats coming from the same cage where they were previously housed were kept during 72 h, with water and food ad lib.

2.4. Experimental procedure

Animals were distributed into six groups (N=20 each). General procedures included previous treatment with saline or venlafaxine (1 or 10 mg/kg) during 10 days associated or not with REMs deprivation. After treatment with drug/saline during 8 days, animals were submitted to 72-h REMs deprivation or remained in their home cages for control. Behavioral tests were performed immediately after the REMs deprivation period. Each experimental group was further divided into two groups (N=10 each). In one set, animals were tested for the plus-maze (5 min) and, after an interval (5 min), the forced swimming test was performed (6 min). The other set of animals was tested for the open-field (4 min) and then for the passive avoidance test. Passive avoidance was performed at two moments on the same animals: immediately after REMs deprivation (15 min after training to assess early memory) and 24 h after, i.e., during the rebound period, to assess late memory. Animal weight was registered in the beginning of drug/saline treatment (day 1), previous to REMs deprivation (day 8) and after REMs deprivation (day 11). Weight obtained on day 11 was subtracted from that obtained on day 8, and this result was used for comparison. One set of animals was sacrificed immediately after the plus-maze and forced swimming tests, and the other set, after open-field and passive avoidance tests (24 h later, i.e., rebound sleep). Striatum from all

animals was dissected, weighted and frozen at −70 °C until monoamine concentration measurements.

2.5. Behavioral tests

2.5.1. The forced swimming test of Porsolt

Based on previous evidence that REMs deprivation is followed by a period of motor stimulation lasting 30 min, as it has been demonstrated in Sprague–Dawley rats (Gessa et al., 1995), we have performed behavior tests within 30 min after interrupting sleep deprivation. According to Porsolt et al. (1978), each rat was placed individually in a transparent acrylic cylinder (50-cm height, 24-cm diameter) containing fresh water (25 °C, 25 cm deep) and was forced to swim for 6 min, and the total immobility duration time (immobility time) was measured. A rat was judged to be immobile whenever it remained floating in the water in a slightly hunched but upright position, with its head just above the surface. The immobility time in all experiments was measured by the same experienced individual.

2.5.2. The plus-maze test

The plus-maze was carried out according to Pellow et al. (1985). The plus-maze consisted of two open (30×5 cm) and two closed (30×5×30 cm) arms, which were connected by a central platform (5×5 cm) elevated 25 cm from the floor. Rats were placed on the central platform facing a closed arm. During a 5-min period, the number of entries made onto the open and closed arms and the time spent in each one were measured. Based on these data, the percentage of entries made onto the open arms and the percentage of time spent onto the open arms were calculated and used for comparison.

2.5.3. Measurement of locomotor activity

The open-field test was used to evaluate locomotor activity (Broadhurst, 1957). Animals were placed in a quadrangular open field (50×50×35 cm), with lines drawn on the floor dividing it in four areas, and after 1 min of adapting period, the number of crossings and rearings were measured during 3 min. Crossing was defined as moving across the lines with at least three feet, and rearing as standing on the hindlegs with the front paws unsupported.

2.5.4. The passive avoidance task

The test was conducted according to DeNoble et al. (1986). A passive avoidance apparatus, consisting of an acrylic box (48×22×22 cm) divided in two compartments, one clear (white acrylic) and other dark (black acrylic), intercommunicated by a window, was used. The clear box was the safe compartment, and the dark was the place where animals received the shock. For training, after a 1-min adapting period, the animals were placed in the clear compartment and received a shock (0.5 mA) as they enter into the dark compartment. After 15 min, the animals were placed again in the clear compartment, and the latency time for entering into the dark compartment was measured (short-term memory), up to a maximum of 5 min. After 24 h, animals were placed again in the clear compartment, and the latency time for entering into the dark compartment was measured to assess long-term memory.

2.6. Determination of brain biogenic amine concentrations

Animals were decapitated immediately after behavioral tests, and the striatum was dissected and kept frozen at −70 °C. Frozen tissues were homogenized in 0.1 N percloric acid and were sonicated for 30 s at 25 °C. After sonication, the samples were centrifuged at 15,000 rpm for 30 min at 4 °C. The supernatants were removed and filtered through a membrane (Millipore, 0.2 μm). Samples were applied to a high-performance liquid chromatograph (Shimatzu) with electrochemical detection (Wagner et al., 1982). A stainless-steel CLC-ODS column (25 cm×4.6 mm) was used. The mobile phase consisted of 0.16 M citric acid, 0.69 M octanosulfonic acid, 4% acetonitrile and 17% tetrahidrofurane. The area of each peak was determined and compared with the peak of the corresponding external standard. Results were expressed as ng/g tissue.

2.7. Statistical analysis

All data are presented as mean±S.E.M. Results were analysed using one-way analysis of variance (ANOVA), followed by Tukey's Multiple Comparison Test, and when

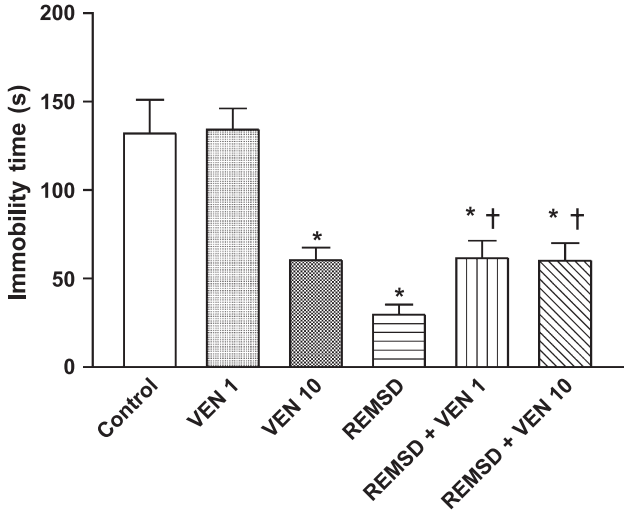

Fig. 1. Effect of venlafaxine on immobility time of REM sleep-deprived rats in the swimming test. Animals were treated with venlafaxine, VEN (1 and 10 mg/kg, p.o.), during 10 days, and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD) or maintained in home cages as control. Values represent mean±S.E.M. of the immobility time during 6 min. *p<0.05 vs. control, $^{\dagger}p$<0.05 vs. REM SD (ANOVA, Tukey's test).

Table 1
Effect of venlafaxine in the plus-maze test of REM sleep-deprived rats

Experimental groups	Open arm		Closed arm	
	Number of entries	Time spent (s)	Number of entries	Time spent (s)
Control	2.40±0.50	35.50±8.35	8.50±1.44	209.40±13.64
Venlafaxine 1 mg/kg	4.60±0.43	58.50±8.73	9.10±0.74	174.60±16.24
Venlafaxine 10 mg/kg	3.90±0.84	37.60±7.84	8.20±0.90	200.20±14.05
REM SD	5.20±0.51*	87.00±10.13*	7.60±0.78	140.70±6.02*
REM SD+Venla 1	6.80±0.74*	80.00±10.67*	10.30±0.67	172.50±10.71
REM SD+Venla 10	4.00±0.87	51.67±13.14†	6.67±0.58	204.20±17.50†

Animals were treated with venlafaxine (1 and 10 mg/kg, p.o.) during 10 days and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD). Values represent mean±S.E.M. of numbers of entries and time spent in each arm of the plus-maze.

* $p<0.05$ vs. control (ANOVA, Tukey's test).

† $p<0.05$ vs. REM SD (ANOVA, Tukey's test).

necessary, we used Student's *t*-test for comparison between two groups. A significance level of 0.05 was applied.

3. Results

3.1. Effect of venlafaxine on swimming activity after REMs deprivation

Fig. 1 shows the effects of venlafaxine and REMs deprivation on the immobility time during the forced swimming test. REMs deprivation alone and venlafaxine (10 mg/kg) both reduced the immobility time when compared with the control group [$F(5,53)=14.38$, $p<0.001$]. Previous treatment with venlafaxine, 1 and 10 mg/kg, reduced the antidepressant effect of REMs deprivation (Student's *t*-test, $p<0.05$).

3.2. Effect of venlafaxine in the elevated plus-maze on REMs deprived rats

REMs deprivation increased significantly [$F(5,53)=4.784$, $p<0.001$] the time spent in the open arm in relation to control (Table 1) and also increased the number of entries [$F(5,53)=6.09$, $p<0.0002$], showing thus an anxiolytic effect. Venlafaxine treatment (1 mg/kg) combined to REMs deprivation increased the number of entries and the time spent in the open arms. Venlafaxine treatment (1 and 10 mg/kg) did not show anxiolytic or anxiogenic properties, however, treatment with 10 mg/kg partially blocked REMs deprivation effects (Table 1).

3.3. Effect of venlafaxine in locomotor activity on REMs deprived rats

REMs deprivation and treatment with venlafaxine, 10 mg/kg, significantly increased the number of crossings [$F(5,53)=7.87$, $p<0.0001$] and rearings [$F(5,53)=6.09$, $p<0.0002$], as shown in Table 2. REMs deprived animals submitted to venlafaxine (10 mg/kg) treatment showed a reduction of locomotor activity in relation to the REMs deprived group (Table 2). Stereotypy was not observed in any group of animals.

Table 2
Effect of venlafaxine in locomotor activity of REM sleep-deprived rats

Experimental groups	Number of crossings	Number of rearings
Control	12.00±1.61	7.10±1.10
Venlafaxine 1 mg/kg	10.60±1.24	6.20±0.69
Venlafaxine 10 mg/kg	19.50±1.49*	11.91±1.31*
REM SD	21.70±2.21*	12.10±1.36*
REM SD+Venla 1	19.67±2.09*	8.11±1.45
REM SD+Venla 10	12.90±1.41†	6.00±0.65†

Animals were treated with venlafaxine (1 and 10 mg/kg, p.o.) during 10 days and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD). Values represent mean±S.E.M. of numbers of entries and time spent in each arm of the plus-maze.

* $p<0.05$ vs. control (ANOVA, Tukey's test).

† $p<0.05$ vs. REM SD (ANOVA, Tukey's test).

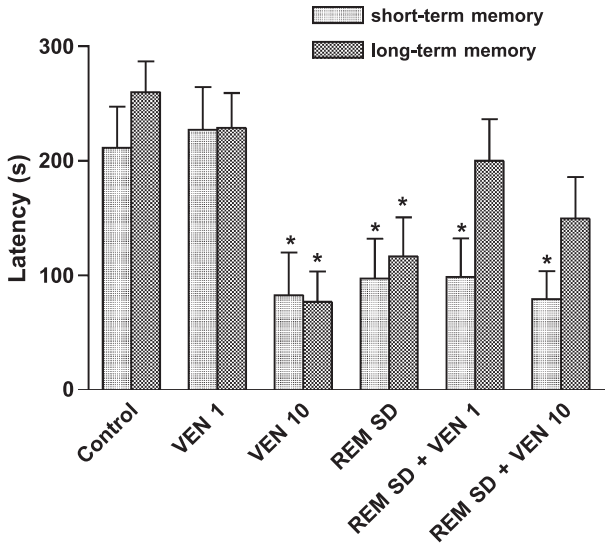

Fig. 2. Effect of venlafaxine on short- and long-term memory of REM sleep-deprived rats in the passive avoidance test. Animals were treated with venlafaxine, VEN (1 and 10 mg/kg, p.o.), during 10 days, and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD) or maintained in home cages as control. Values represent mean±S.E.M. of the latency time to enter in the dark side of the passive avoidance apparatus. *$p<0.05$ vs. control (ANOVA, Tukey's test).

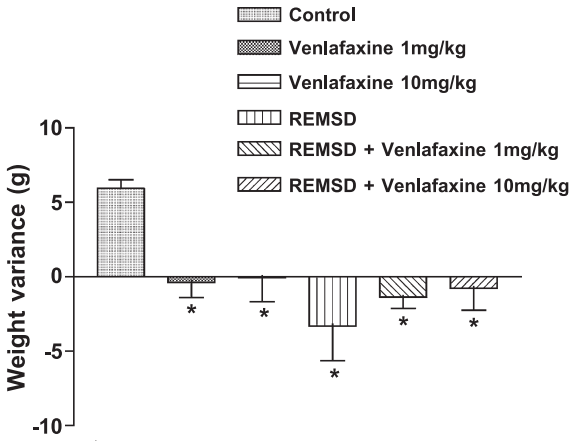

Fig. 3. Effect of venlafaxine on the body weight of REMs deprived rats. Animals were treated with venlafaxine, VEN (1 and 10 mg/kg, p.o.), during 10 days, and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD) or maintained in home cages as control. Values represent mean±S.E.M. of the weight variance between the 8th and 11th days of treatment. *p<0.05 vs. control (ANOVA, Tukey's test).

3.4. Effect of venlafaxine on short- and long-term memory of REMs deprived rats

Differences in performances were observed among groups in short- [$F(5,53)=3.94$, $p<0.004$] and long-term memory [$F(5,53)=4.84$, $p<0.001$]. Fig. 2 shows that the control group (saline-treated animals) increased significantly the latency time to enter in the dark side after 15 min and 24 h, respectively, for short- and long-term memory. Rats treated with venlafaxine, 1 mg/kg, also demonstrated good memory acquisition. We observed an impairment of memory acquisition on REMs deprived and on venlafaxine (10 mg/kg)-treated rats when compared with the control. REMs deprived rats treated with venlafaxine (1 and 10 mg/kg) also showed short-term memory acquisition impairment ($p<0.05$).

Table 3
Effect of venlafaxine on dopamine and metabolites concentrations in the striatum of REM sleep-deprived rats

Experimental groups	DA	DOPAC (DOPAC/DA)	HVA (HVA/DA)
Control	789.8±239.6	363.4±208.8 (0.51±0.13)	222.3±56.0 (0.32±0.08)
Venlafaxine 1 mg/kg	548.9±392.1	798.4±154.9 (0.44±0.05)	91.7±33.5 (0.55±0.38)
Venlafaxine 10 mg/kg	3165.0±748.1*	510.7±128.5 (0.21±0.04)*	423.8±122.7 (0.30±0.20)
REM SD	1547.0±530.0	893.2±117.6 (0.56±0.14)	286.1±59.9 (0.25±0.06)
REM SD+ Venla 1	917.5±155.7	287.5±27.2† (0.36±0.07)	93.7±12.3† (0.12±0.03)
REM SD+ Venla 10	804.3±138.3	488.4±139.4 (0.63±0.17)	162.5±37.3 (0.24±0.05)

Animals were treated with venlafaxine (1 and 10 mg/kg, p.o.) during 10 days and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD). Values represent mean±S.E.M. of DA, DOPAC and HVA concentrations, expressed as ng/g tissue. Numbers between parenthesis represent DOPAC/DA and HVA/DA ratio.

* p<0.05 vs. control (ANOVA, Tukey's test).

† p<0.05 vs. REM SD (ANOVA, Tukey's test).

Table 4
Effect of venlafaxine on serotonin and 5-HIAA concentrations in the striatum of REM sleep-deprived rats

Experimental groups	Serotonin	5-HIAA (5-HIAA/5-HT)
Control	169.2±53.1	179.2±79.9 (0.56±0.06)
Venlafaxine 1 mg/kg	328.9±135.6	231.1±95.7 (0.73±0.05)
Venlafaxine 10 mg/kg	328.9±88.46	217.0±45.81 (0.61±0.12)
REM SD	256.4±64.7	150.9±25.4 (0.71±0.17)
REM SD+Venla 1	414.9±125.5	33.1±5.8† (0.15±0.09)†
REM SD+Venla 10	235.2±60.9	109.9±48.5 (0.93±0.32)

Animals were treated with venlafaxine (1 and 10 mg/kg, p.o.) during 10 days and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD). Values represent mean±S.E.M. of 5-HT and 5-HIAA concentrations, expressed as ng/g tissue. Numbers between parenthesis represent 5-HIAA/5-HT ratio.

† p<0.05 vs. REM SD (ANOVA, Tukey's test).

3.5. Effect of venlafaxine on the body weight of REMs deprived rats

Significant [$F(5,53)=3.94$, $p<0.004$] weight loss was observed in association with venlafaxine treatment and after REMs deprivation (Fig. 3). The combination of venlafaxine treatment and REMs deprivation showed a trend for reversal of weight loss associated with REMs deprivation.

Table 5
Effect of venlafaxine on dopamine and metabolites concentrations of rats after 24 h of REM sleep deprivation

Experimental groups	DA	DOPAC (DOPAC/DA)	HVA (HVA/DA)
Control	798.7±173.1	363.9±84.1 (0.46±0.04)	181.0±34.8 (0.28±0.07)
Venlafaxine 1 mg/kg	2995.0±325.4	2171.0±48.6* (0.76±0.08)	479.6±87.5* (0.16±0.03)
Venlafaxine 10 mg/kg	6372.0±1678.0*	69.7±50.1 (0.22±0.09)	111.6±21.6* (0.04±0.02)
REM SD	1258.0±330.3	1081.0±225.5* (0.91±0.17)*	202.9±63.7 (0.17±0.04)
REM SD+ Venla 1	2758.0±470.6	1946.0±170.9*,† (0.76±0.10)	614.9±76.2* (0.23±0.02)
REM SD+ Venla 10	1338.0±162.7	1519.0±91.1* (1.22±0.19)*	396.6±37.8*,† (0.30±0.02)†

Animals were treated with venlafaxine (1 and 10 mg/kg, p.o.) during 10 days and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD). Values represent mean±S.E.M. of DA, DOPAC, and HVA concentrations, expressed as ng/g tissue. Numbers between parenthesis represent DOPAC/DA and HVA/DA ratio.

Table 6
Effect of venlafaxine on serotonin and 5-HIAA concentrations of rats after 24 h of REM sleep deprivation

Experimental groups	Serotonin	5-HIAA (5-HIAA/5-HT)
Control	122.7±27.9	98.5±22.7 (0.85±0.10)
Venlafaxine 1 mg/kg	52.6±25.4	141.9±34.9 (4.08±2.35)
Venlafaxine 10 mg/kg	213.7±99.4	213.6±73.0 (0.96±0.06)
REM SD	298.0±76.8	378.6±85.6* (1.09±0.34)
REM SD+Venla 1	188.5±52.9	560.7±107.2*,† (3.82±0.96)†
REM SD+Venla 10	246.0±24.4	358.8±43.1 (1.46±0.09)

Animals were treated with venlafaxine (1 and 10 mg/kg, p.o.) during 10 days and, on the eighth day of treatment, were submitted to 72 h of REM sleep deprivation (REM SD). Values represent mean±S.E.M. of 5-HT and 5-HIAA concentrations, expressed as ng/g tissue. Numbers between parenthesis represent 5-HIAA/5-HT ratio.

* $p<0.05$ vs. control (ANOVA, Tukey's test).

† $p<0.05$ vs. REM SD (ANOVA, Tukey's test).

3.6. Effect of venlafaxine on concentration of monoamines and metabolites of REMs deprived rats

Venlafaxine (10 mg/kg) treatment produced an increase [$F(5,56)=5.05$, $p<0.001$] in dopamine levels (Table 3), and REMs deprivation did not alter this concentration. Dihydroxyphenylacetic acid [DOPAC; $F(5,20)=24.70$, $p<0.0001$] and homovanillic acid [HVA; $F(5,21)=10.43$, $p<0.0001$], the dopamine (DA) metabolites, showed a significant ($P<0.05$) increase during rebound sleep, after 24 h REMs deprivation, in venlafaxine-treated rats (Table 5). Conversely, venlafaxine and REMs deprivation produced no significant increase in 5-hydroxytryptamine (5-HT) concentration. After 24 h of REMs deprivation and venlafaxine (10 mg/kg) treatment, an increase [$F(5,26)=5.89$, $p<0.0009$] in 5-hydroxyindolacetic acid (5-HIAA) concentration (Table 6) was observed. The DOPAC/DA ratio was not affected after REMs deprivation, but venlafaxine (10 mg/kg) treatment alone decreased DA turnover (Table 3). We observed a decrease of the 5-HIAA/5-HT ratio after venlafaxine treatment (1 mg/kg) in REMs deprived rats (Table 4). A significant increase in DA [$F(5,56)=8.63$, $p<0.001$; Table 5] and 5-HT [$F(5,24)=2.87$, $p<0.03$; Table 6] turnover was observed 24 h after REMs deprivation in venlafaxine-treated rats.

4. Discussion

REMs deprivation has been clinically shown to improve certain types of depression in humans (Vogel, 1975; Larsen et al., 1976). In rodents, this treatment decreases the immobility time in forced swimming test, an animal model for screening of antidepressive drugs (Porsolt et al., 1978; Hawkins et al., 1980). Similar to previous reports (Brock et al., 1994; David et al., 2001), our experiments showed that REMs deprivation and venlafaxine treatment had an antidepressant effect. Previously, a potentiation of the antidepressant effect of REMs deprivation was shown in association with imipramine and desipramine but not with clomipramine (Asakura et al., 1993). In our experiment, venlafaxine treatment reduced REMs deprivation effects. This drug selectively inhibits the uptake of serotonin and noradrenaline. In addition, another report suggests that REM sleep deprivation renders the serotonergic dorsal raphe nucleus less sensitive to the inhibitory effect of 5-hydroxytryptamine (5-HT) re-uptake blockers, probably due to the functional desensitization of somatodendritic 5-HT1A autoreceptors (Maudhuit et al., 1996).

An increase in the parameters related to the open arm of the plus-maze was demonstrated after REMs deprivation and REMs deprivation associated with venlafaxine 1, but not 10, mg/kg treatment. This effect is most likely to be due to an anxiolytic effect of REMs deprivation rather than to motor stimulation, as the number of entries in the closed arm was not increased. These results are in accordance with other reports that show less anxiety-like behavior in REMs deprived rats (Suchecki et al., 2002). It has also been shown that low doses of venlafaxine act preferentially on the 5-HT system, while higher doses inhibit both 5-HT and NE re-uptake (Redrobe et al., 1998). Furthermore, an increase in locomotor activity associated with REMs deprivation has been observed previously by other authors (Ghosh et al., 1976; Van Hulzen and Coenen, 1980). In the current study, this effect was reduced by venlafaxine treatment. Asakura et al. (1994) showed that the increased swimming activity after REMs deprivation is mainly due to functional changes in dopaminergic system rather than in noradrenergic or serotonergic system, and that a dopamine D2, but not D1, receptor mechanism is involved is this action. Ghosh et al. (1976) also demonstrated that, in REMs deprived rats, the concentration of striatal dopamine was increased after 4 days. Other reports showed that, in REMs deprived rats, supersensitivity to dopaminergic receptor agonists (Tufik et al., 1978; Troncone et al., 1988) may be reversed by pretreatment with some dopaminergic agonists. Increased dopamine levels after venlafaxine treatment (Ellingrod and Perry, 1994; Rockville, 1994) may be a possible explanation for the reversal of REMs deprivation effects after venlafaxine treatment.

Previous reports have demonstrated weight loss in REMs deprived rats despite increased food intake (Gilliland et al., 1989; Kushida et al., 1989), this probably due to the increased energy expenditure. On the contrary, most antidepressants appear to produce weight gain after 6–12 months of therapy (Masand and Gupta, 2002). The exception is venlafaxine, which appears to be associated with a weight decrease (Jackson et al., 1997; Kraus et al., 2002). In our experiments, REMs deprived rats showed weight loss, which was partially reverted by venlafaxine treatment.

In the current study, REMs deprivation is associated with impairment of memory acquisition on the passive avoidance test, and these results are in accordance with previous works that have shown deficit in spatial memory (Youngblood et al., 1999) or inhibitory avoidance (Bueno et al., 2000). Our results also show that venlafaxine treatment in higher (10 mg/kg), but not in lower (1 mg/kg), doses induced memory impairment. The literature is controversial about memory impairment induced by antidepressive treatment. After tryciclic antidepressants use, both no effect (Hindmarch et al., 2000) and impaired memory formation (Amado-Boccara et al., 1994; Stip et al., 2000) have been described. The glutamatergic, cholinergic, serotonergic and dopaminergic systems have an important role on memory formation (Izquierdo et al., 1998), thus changes in monoamine neurotransmitters concentrations in rat forebrain regions (frontal and parietal cortices, hippocampus and striatum) induced by REMs deprivation and antidepressants can explain memory impairment.

The literature has shown an increased 5-HT metabolism after REMs deprivation (Toru et al., 1984; Youngblood et al., 1999). In our work, the dopamine turnover in the striatum remained unchanged in REMs deprived rats and after venlafaxine treatment, but it was increased 24 h after rebound sleep. On the other hand, the serotonin turnover that was decreased after REMs deprivation showed a significant increase 24 h after rebound sleep in venlafaxine-treated animals. These results suggest that REMs deprivation alters dopaminergic and serotonergic systems, and this effect could be changed by antidepressants.

Anxiety and depressive disorders are more common among women in adult life (Pearson, 1995; Gold, 1998; Patel et al., 1999). As this study was conducted in female rats, it must be mentioned that sleep homeostasis is modulated by the estrous cycle (Zhang et al., 1995). It has also been demonstrated that the ovarian cycles of female rats become synchronized when they live together, as do the cycles of many other mammals, and ovarian cycles also become synchronized when rats live apart, if they share a common air supply, indicating that ovarian-cycle synchrony is mediated by pheromones (Schank and McClintock, 1992).

In conclusion, our results show that the behavioral effects produced by REMs deprivation, i.e., anxiolytic, antidepressive, locomotor and weight loss, can be reversed by venlafaxine treatment. These findings might be explained by interference on the dopaminergic or serotonergic systems. Differential actions between the several classes of antidepressants may influence the therapy of depression, particularly in clinical conditions associated with sleep deprivation.

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