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Effect of Chronic Mild Stress on Circadian Rhythms in the Locomotor Activity in Rats

ZBIGNIEW GORKA[1] ELZBIETA MORYL AND MARIUSZ PAPP

Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna St., 31-343 Krakow, Poland

GORKA, Z., E. MORYL AND M. PAPP. *Effect of chronic mild stress on circadian rhythms in the locomotor activity in rats.* PHARMACOL BIOCHEM BEHAV **54**(1) 229–234, 1996.—The purpose of this study was to assess whether the chronic mild stress (CMS) procedure, as a realistic animal model of depression, affects the rhythms of the locomotor activity in rats. Rhythm parameters (period, mesor, amplitude, acrophase, and percent rhythm) were estimated from the best-fitted cosine function curves. Period is the length, mesor is the mean level, amplitude (A) is the extent, acrophase is the timing of the rhythm; percent rhythm represents the variability estimated by the cosine regresion and expressed as a percentage of the total variability of raw data. The animals were kept on the 12 L : 12 D cycle during 13 weeks of the experiment and subjected to CMS for first 4 weeks. In week 5 the rats were under the constant light for 24 h a day (LL), and in week 9, under the constant darkness (DD). In LD 12 : 12 CMS decreased the activity in the dark phase by approximately 50% ($p < 0.01$) and did not change the activity in the light phase, resulting in a drop of the 24 h activity by about 40% in comparison to controls. The amplitude of diurnal variations of the activity was highly statistically different from zero at $p(A = 0) < 0.0001$, and the percent rhythm was in range of 40–75% in both the CMS and control groups. The mesor and the amplitude of the diurnal rhythm (with a period of 24 h) in the CMS rats were significantly ($p < 0.001$) lower than those in the control. In LL, the activity of both groups was diminished about 50% during the subjective dark phase. On the other hand, in the subjective light phase the activity of CMS rats only was diminished. The percent rhythm for the CMS and control rats was 30 and 58%, respectively, and values of mesor, amplitude, and acrophase for both groups were highly statistically different. In DD, the activity in the CMS group was statistically significantly lower in both the subjective dark and light phases. In contrast to the results from LL, the cosine curves from DD were similarly shifted in relation to the subjective light-dark cycle. After a restoration of the LD cycle the levels of the 24-h activity of both groups became equal in the 13th week, but the light and dark phase differences between the groups were still statistically significant ($p < 0.05$). The present results indicate that CMS exerts distinct and prolonged disturbances of the diurnal and circadian rhythms of the locomotor activity in the rats.

Chronic mild stress Circadian rhythms Locomotor activity Rats

ANTIDEPRESSANT drugs (AD) have been used for the treatment of depressed patients for almost 40 years (5,12,15), yet both the etiopathology of depression and the mechanisms of the therapeutic actions of these drugs are not clear. It is commonly known that AD do not improve mood in healthy people, and the pharmacological studies on AD carried out on normal animals may not detect these properties of AD, which are causally connected with their therapeutic activity in patients. Hence, it seems crucially important to carry out the studies on mechanisms of depressive illness and its treatment in experimental models of depression. One of such animal models is a chronic mild stress paradigm (35). In this model, rats subjected to a variety of mild stressors for a prolonged period of time show a substantial decrease in their responsiveness to rewarding stimuli (anhedonia). According to DSM III (1), anhedonia is one of two core symptoms of major depression, and can be realistically modeled in animals. AD after repeated treatment restore normal reactivity in both depressed patients and depressed rats (20,35). Several clinical observations suggest that there is an association between the pathophysiology of affective disorders and disturbances of circadian rhythms in humans (4,7,9–11). It has been shown a variety of abnormalities in the period, phase and amplitude of many physiological, behavioral, and endocrine rhythms of manic depressive and depressed patients (13,14,26–29,32–34). Disordered rhythms have been observed also in some putative animal models of depression (2,6,8,24,30). Moreover, it has been reported, that several AD, with different pharmacological mechanisms of action, can influence circadian rhythms in humans and in laboratory animals (7,10,13,34,36,37). In this context, we decided to investigate whether CMS, as a realistic model of depression, affects the diurnal rhythm of locomotor activity in rats housed in the 12 L : 12 D cycle and the circadian rhythms of the activity in rats kept either in the continu-

[1] To whom requests for reprints should be addressed.

ous light or continuous darkness. A demonstration of the phenomenological similarity between the rhythm effects of the CMS procedure and depression would increase the face validity of the model, on one hand, and would speak in favor of the contribution of the rhythm disturbances in the pathogenesis of depression, on the other hand.

METHOD

Animals and Housing

Experiments were carried out on male Wistar rats, 3 months old, weighing 260–280 g of body weight at the start of the experiment, with free access to granulated food (LSM Motycz) and tap water. The rats were housed individually in polycarbonate cages (Macrolon, 56 × 36 × 20 cm) under controlled environmental conditions (the 12 L : 12 D cycle, lights on at 0700 h, room temperature 21–23°C) for 2 weeks before the start of the CMS procedure. The animals were randomly divided into CMS and control groups and were kept in separate rooms. The intensity of illumination was 200 lx in the light phase and <0.1 lx in the dark phase.

Experimental Protocol

The CMS rats were subjected to the sequential application of a variety of mild stressors for 5 days of each week during first 4 weeks of experiments, which lasted 13 weeks. The stress regime was similar to that used previously (20) and consisted

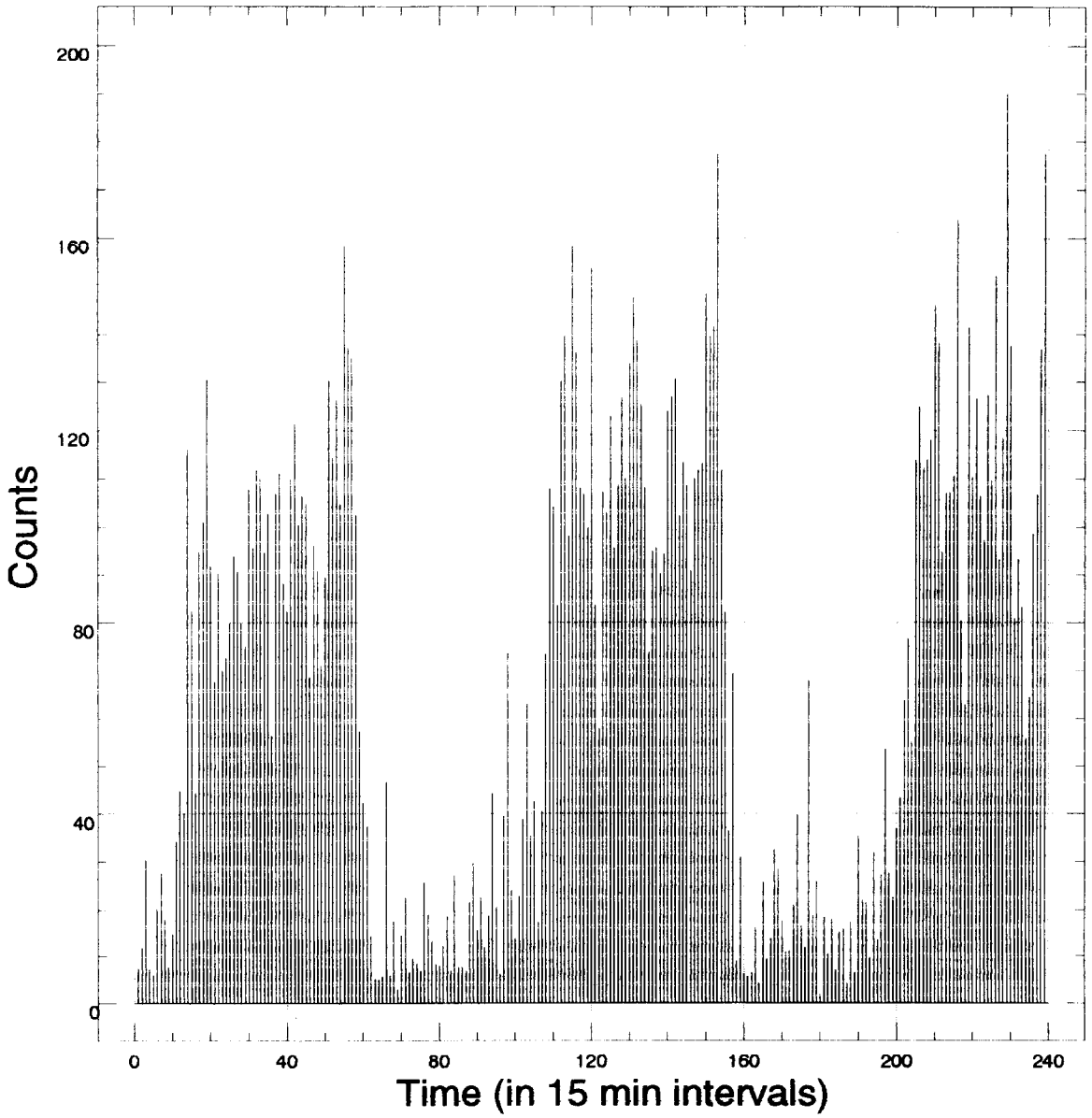

FIG. 1. The representative time plot of the locomotor activity in the control rats kept in the 12 L : 12 D cycle. The graph ordinate denotes the mean values of the activity in counts recorded in 15-min intervals for eight rats. Abscissa denotes time of 240 intervals.

TABLE 1

THE LOCOMOTOR ACTIVITY (MEAN ± SEM, IN THOUSANDS) IN THE CONTROL (Con) AND STRESSED (CMS) RATS

Week No	Lighting Cycle	Group	Dark	Light Activity	24 Hour
1	LD 12 : 12	Con	3.5 ± 0.5	1.9 ± 0.2	5.4 ± 0.6
		CMS	1.7 ± 0.2*	1.9 ± 0.4	3.6 ± 0.5†
3	LD 12 : 12	Con	5.0 ± 0.3	0.8 ± 0.1	5.8 ± 0.3
		CMS	2.3 ± 0.3‡	1.0 ± 0.2	3.4 ± 0.5*
5	LL	Con	2.6 ± 0.2	2.2 ± 0.1	4.9 ± 0.2
		CMS	1.4 ± 0.3*	0.9 ± 0.2‡	2.4 ± 0.5*
7	LD 12 : 12	Con	4.2 ± 0.1	0.7 ± 0.2	5.0 ± 0.3
		CMS	2.6 ± 0.3‡	0.7 ± 0.2	3.2 ± 0.5*
9	DD	Con	3.4 ± 0.1	1.7 ± 0.1	5.2 ± 0.1
		CMS	2.2 ± 0.3*	1.2 ± 0.2†	3.4 ± 0.4*
11	LD 12 : 12	Con	3.8 ± 0.3	1.7 ± 0.1	5.5 ± 0.3
		CMS	2.2 ± 0.2*	1.1 ± 0.2†	3.3 ± 0.3‡
13	LD 12 : 12	Con	3.7 ± 0.1	0.7 ± 0.1	4.4 ± 0.1
		CMS	3.2 ± 0.2†	1.2 ± 0.2†	4.4 ± 0.3

*$p < 0.001$; †$p < 0.05$; ‡$p < 0.001$ relative to controls, Dunnett's t-test; $n = 8$/group.

of 12-h periods of paired housing, food and/or water deprivation, stroboscopic illumination, and a 15-min period of immersion in a cylinder containing water 15 cm high at 25°C. The animals placed into cylinders, after short periods of vigorous activity to escape, quickly assumed a characteristic floating posture, with small movements necessary to keep their heads just above the surface of water. The rats were almost complete immobile for approximately 80% of the 15-min period. The control rats were left undisturbed. In the 5th week all the rats were kept under the constant light 24 h a day (LL); in the 9th week, under the constant darkness (DD).

Apparatus and Data Collection

The locomotor activity was continuously monitored in home cages over the 24-h span and recorded at 15-min intervals using an animex apparatus and an IBM-PC/XT computer system throughout the experiment. When a rat moves, each animal's movement activates the inductive-capacitative circuit of the animex actometer and the interface logic, located in an adjacent room, generates a single count. Every 100 ms the computer samples the status of the actometer system and the data are recorded on the hard disk of the computer and stored in its memory for further statistical analysis.

Statistical Analysis

All the obtained values in counts were calculated as the means ± SEM of eight animals per group. The statistical significance of differences in the activity between groups was assessed by the Dunnett's t-test. The statistical validation and quantification of the rhythm parameters for time series were done by the best fitting cosine function using the Cosina program (17). The parameters (period, mesor, amplitude and acrophase) were defined by the equation: $y(t_i) = M + A \cos(\omega t_i + \phi) + e_i$, where $i = 1, \ldots, n$; $y(t_i)$ is the observed value of the variable at time t_i; M (mesor, *m*idline *e*stimating *s*tatistic *o*f *r*hythm) is the mean level, A (amplitude) is the extent, ϕ (acrophase) is the timing of the rhythm; ω is the angular velocity, which is related to the period (τ) by the equation: $\tau = 2\pi/\omega$; n is the number of readings in the time series; and e_i is the residual error about the sinusoid (i.e., mismatch between sinusoid and data) at time t_i.

RESULTS

Locomotor Activity

Figure 1 shows a representative recording of the locomotor activity in control rats. The effect of CMS on the locomotor activity of the rats in 13 consecutive weeks of the experiment is presented in Table 1 as the activity in the dark and light phases of the diurnal cycle and as the 24 h activity of the stressed rats in comparison to the control group. During first 4 weeks CMS decreased the activity in the dark phase by approximately 50% ($p < 0.01$) and did not change the activity in the light phase, resulting in a drop of the 24 h activity by about 40% in comparison to controls. In LL conditions the activity of both groups was diminished about 50% during the subjective dark phase. On the other hand, in the subjective light phase the activity of the stressed rats only was diminished. In DD conditions the activity of the CMS was statistically significantly lower than that of the control in both the subjective dark and light phases. After a restoration of the 12 L : 12 D cycle of illumination the levels of the 24-h activity of both groups became equal in the 13th week, but the light and dark phase differences between the groups were still statistically significant (Table 1).

Diurnal and Circadian Rhythms

The effect of CMS on the diurnal (in LD) and circadian (in LL or DD) rhythms of the locomotor activity is presented in Figs. 2-6 and Table 2. During first 4 weeks the amplitude of diurnal variations of the activity was highly statistically different from zero at $p(A = 0) < 0.0001$ and the percent rhythm was in range of 40-75% in both the CMS and control groups. After the 4th week the percent rhythm for the CMS and control rats was 42 and 43%, respectively, $p(A = 0) < 0.0001$. However, the mean activity and the amplitude of the diurnal rhythm (with a period of 24 h) in the CMS rats were significantly ($p < 0.001$) lower than those in the control, (Fig.

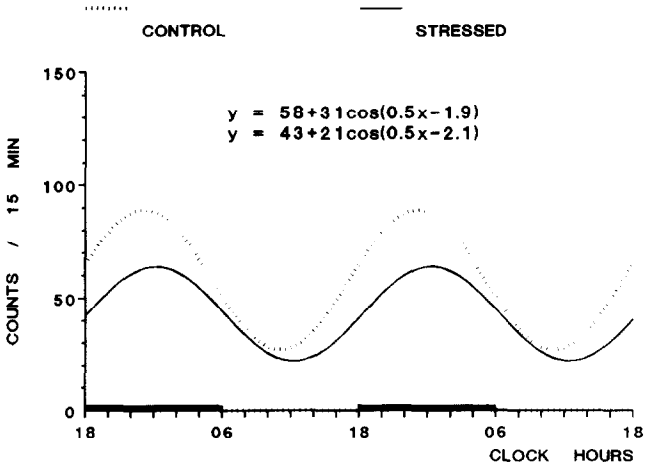

FIG. 2. The diurnal rhythm of the locomotor activity in the control (dotted line) and stressed (solid line) rats, kept in the 12 L : 12 D cycle after the 4th week of CMS. The equations describe the cosine curves best fitted to the raw data. Ordinate denotes the mean values of the activity in counts per 15 min for eight rats. Abscissa—time in clock hours, thick and thin segments indicate the dark (1800–0600 h) and light (0600–1800 h) phases of the LD cycle, respectively.

2). In LL, a free-running rhythm (with a period longer than 24 h) was observed in the activity of both groups (Fig. 3). The percent rhythm for the CMS and control rats was 30 and 58%, respectively. The cosine curves were fitted to the raw data from the last 3 days of the 5th week, and different values of the mean activity (in counts), amplitude (in counts), and acrophase (in hours, from the beginning of the subjective dark phase) were obtained for the CMS and control rats. The differences between the groups for all the parameters were highly statistically significant (Table 2). In the next week, the 12 L : 12 D cycle of illumination was reimposed and both groups of the rats were kept in that LD schedule for 3 weeks. During that period the basal rest-activity cycle of all rats became

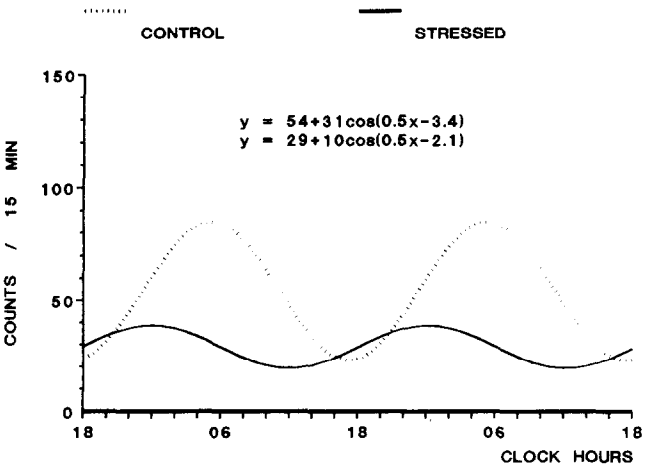

FIG. 3. The circadian rhythm of the locomotor activity in the control (dotted line) and stressed (solid line) rats, kept in the LL cycle, after the 5th week. The equations describe the cosine curves best fitted to the raw data. Ordinate denotes the mean values of the activity in counts per 15 min for eight rats. Abscissa—time in clock hours.

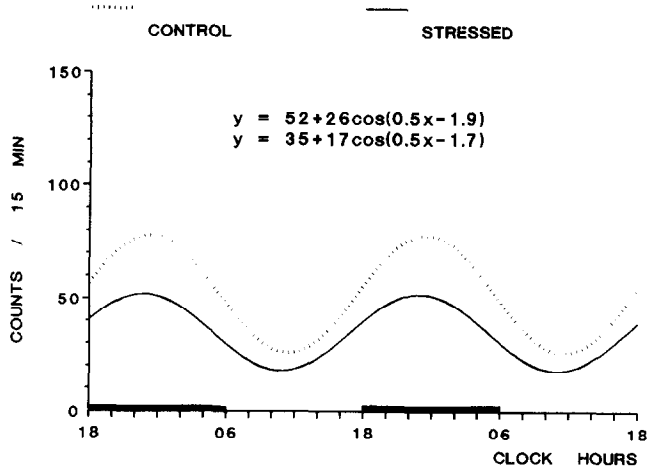

FIG. 4. The diurnal rhythm of the locomotor activity in the control (dotted line) and stressed (solid line) rats, kept in the 12 L : 12 D cycle, after the 7th week. For other explanations, see Fig. 2.

resynchronized with the LD cycle, and the parameters of the rhythm in the respective groups reached values similar to those that were observed at the end of the CMS period. However, the mean activity and amplitude of the rhythm in the CMS rats were still significantly lower than those in the control group (Fig. 4). At the beginning of the 9th week the LD schedule was changed again and all rats were put under continuous darkness conditions for 1 week. Also in DD a free-running rhythm appeared in the activity of both groups (Fig. 5). In contrast to the results from LL conditions, the cosine curves fitted to the data of both groups from the last 3 days of DD were similarly shifted in relation to the subjective light-dark cycle (Fig. 5). A comparison of the parameters of the circadian activity rhythm in both groups revealed that the mean activities and the amplitudes, but not the acrophases, of the rhythms were statistically different (Table 2). After a reimposition of the 12 L : 12 D cycle of illumination a gradual resynchronization of the activity rhythms to the LD cycle was

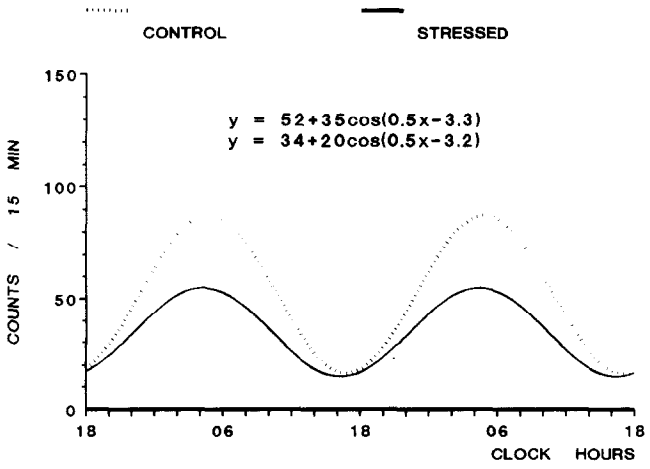

FIG. 5. The circadian rhythm of the locomotor activity in the control (dotted line) and stressed (solid line) rats, kept in the DD cycle, after the 9th week. For other explanations, see Fig. 3.

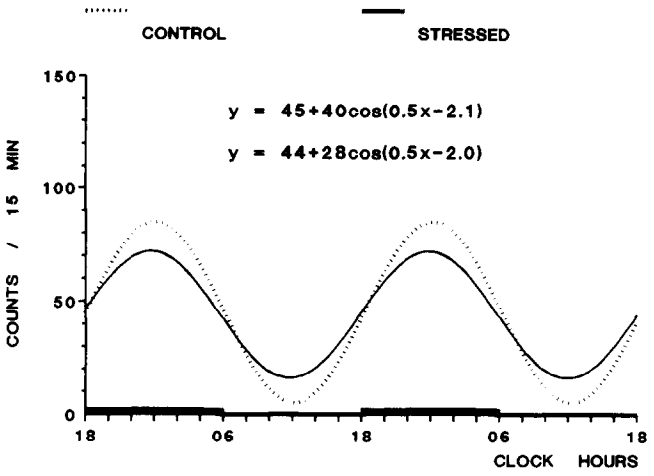

FIG. 6. The diurnal rhythm of the locomotor activity in the control (dotted line) and stressed (solid line) rats, kept in the 12 L : 12 D cycle, after the 13th week. For other explanations, see Fig. 2.

observed in the CMS and control rats again, but the differences in the mean activity and amplitude between both groups were still statistically significant (Table 2). At the end of the 13th week (when the monitoring of the activity of all rats was finished) the percent rhythm for the activity of the CMS and control groups was 61 and 70%, respectively, at probability of zero amplitude $p(A = 0) < 0.0001$. The cosine curves for the data from the CMS and control groups were different in amplitude but not in the mean activity or acrophase (Fig. 6).

DISCUSSION

The purpose of this study was to determine whether the CMS procedure, regarded as a realistic animal model of depression, would influence not only the level of the locomotor activity but, first of all, the rhythmic structure of the behavior in the rats. Previously, it has been demonstrated that CMS-treated rats are subsensitive to the rewarding properties of a variety of natural and drug rewards, as assessed in the consumption of solutions of sucrose and in the place preference conditioning (19,22,35). CMS has also been reported to decrease sensitivity to brain stimulation reward, as assessed by the threshold current required to support intracranial self-stimulation (18). The present results indicate that CMS exerts distinct and prolonged disturbances of the diurnal and circadian rhythms of the locomotor activity in the rats. In the conditions of the strong synchronizer, which is the LD cycle, a considerable decrease of the activity in the stressed rats is observed in the dark, but not in the light phase of the diurnal cycle. Noteworthy, that if an activity would be evaluated in the light phase of the cycle only, as it is carried out in the majority of pharmacological tests, such a lack of any effect in one phase might be misinterpreted as a total ineffectiveness of a method due to, for example, too weak stress factors. This earlier mentioned decrease of the activity is visible also in both significantly reduced the mean activity and the amplitude of the diurnal rhythm. The diminution of both parameters of the rhythm persists until the 13th week. The most evident differences between the stressed and control groups in terms of rhythm parameters appear in LL, in free-running rhythm conditions. The rhythms of the activity in both groups start to drift in relation to the subjective LD cycle because the synchronizer is absent. As a result, a phase shift is seen in both the rhythms. However, the rate of the desynchronization in both groups must be different because the cosine curves are not parallel shifted. Also in DD the activity rhythms in both groups free run and the time points of the highest activity on the curves (acrophases) are shifted in relation to the subjective LD cycle. But in contrast to the LL conditions the phase shift of the cosine curves for the stressed and control rats is similar. The mechanism of these effects is not clear. The suprachiasmatic nucleus (SCN) is thought to be the pacemaker responsi-

TABLE 2

THE RHYTHM PARAMETERS (MEAN ± SEM) BEFORE, DURING, AND AFTER CMS IN THE CONTROL (Con) AND STRESSED (CMS) RATS

Week No	Lighting Cycle	Group	Mesor (Counts)	Amplitude (Counts)	Acrophase (Hours)
−1	LD 12 : 12	Con	63.0 ± 2.0	42.8 ± 1.6	6.9 ± 0.1
		CMS	64.0 ± 2.2	43.2 ± 1.8	6.9 ± 0.1
1	LD 12 : 12	Con	62.7 ± 2.3	43.0 ± 3.2	7.2 ± 0.3
		CMS	44.4 ± 1.4*	22.7 ± 1.8*	9.0 ± 0.4†
3	LD 12 : 12	Con	58.2 ± 2.4	31.2 ± 3.7	3.6 ± 0.4
		CMS	43.4 ± 1.6*	20.8 ± 2.5‡	4.1 ± 0.4
5	LL	Con	53.7 ± 1.1	30.7 ± 1.5	6.6 ± 0.2
		CMS	28.9 ± 0.6*	9.6 ± 0.9*	4.0 ± 0.3*
7	LD 12 : 12	Con	51.7 ± 2.3	26.1 ± 3.5	3.6 ± 0.4
		CMS	34.6 ± 1.4*	17.0 ± 2.1‡	3.3 ± 0.4
9	DD	Con	51.8 ± 2.1	35.5 ± 3.0	6.3 ± 0.3
		CMS	34.4 ± 1.4*	19.7 ± 2.0*	6.1 ± 0.4
11	LD 12 : 12	Con	55.8 ± 1.3	51.7 ± 1.8	2.4 ± 0.1
		CMS	36.8 ± 1.0*	27.2 ± 1.4*	2.5 ± 0.2
13	LD 12 : 12	Con	44.9 ± 1.1	39.9 ± 1.6	4.1 ± 0.1
		CMS	44.0 ± 0.9	28.2 ± 1.3*	4.0 ± 0.2

*$p < 0.001$; †$p < 0.01$; ‡$p < 0.005$, relative to controls, Dunnett's t-test, $n = 8$/group.

ble for generating circadian rhythms (25), so the disturbance of behavioral rhythmicity in the stressed rats seems to be associated with functional changes of the circadian pacemaker. The SCN contains high-affinity melatonin receptors (31) and is physiologically affected by melatonin in vivo and in vitro (3,16). The disorganization of circadian rhythms in the locomotor activity produced by CMS, particularly in the LL conditions, may be due to loss of melatonin production by the pineal, because light suppresses melatonin production (3,4, 14), and LL-disrupted rhythms can be reinstated by daily injection of melatonin (3,23). It seems that this study provides further evidence in favor of the hypotheses relating affective disorders to disturbances of circadian rhythms in patients (7,9,11,16,26,29). Further studies are needed to answer the question whether antidepressant drugs counteract the effects of CMS on the diurnal and circadian rhythms.

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