Effect of Unilateral Inactivation of Cerebral Hemisphere on Rhythmic Nociception Variations in Mice

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Changes in the biological rhythms of nociception in the circadian and ultradian range were studied with thermal noxious heat and tail-flick test in mice subjected to unilateral inactivation of cerebral hemispheres. Spectral analysis showed that sham operation suppresses initial circadian rhythm but augmens the amplitude of 12-h rhythm against this background. During isolated activity of the right hemisphere, the high-power circadian rhythm was restored, although its phase and that of the 12-h rhythm were inverted. During isolated activity of the left hemisphere, the acrophase of circadian rhythm (occurring in the middle of daytime) coincided with that in intact mice, although the frequency of ultradian rhythms was increased. Our data attest to existence of functional interhemisphere asymmetry in regulation of mice nociception rhythm which is characterized by the dominant role of the left hemisphere. Such individual functional features of cerebral hemispheres are not manifested in the averaged daily data, but they can be revealed by the chronobiological methods.

Key Words: *nociception; circadian rhythms; interhemisphere asymmetry*

As most physiological functions, the level of nociceptive sensitivity, degree of pain syndrome, and frequency of its manifestation vary during a day in animals [4,9-11] and in humans [12,13]. At present, the neurophysiological mechanisms that regulate the rhythmicity of nociception are unknown. We assumed that most circadian rhythms have stable phasic relationships with the sleep-wakefulness cycle. The state of brain cortex is an important component of these relationships. Many cortical areas participate both in primary perception, qualitative evaluation of noxious stimuli, and formation of integrative nocifensive reactions [1]. We studied the role of brain cortex in the regulation of nociception rhythmicity. Taking into account numerous data on interhemisphere functional asymmetry [5,6], we studied the effects of isolated activity of the right and left cerebral hemispheres (RCH and LCH, respectively).

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MATERIALS AND METHODS

Experiments were carried out on mature male SHR mice. During 4 weeks before experiment, the mice were kept under controlled illumination. The light phase continued from 9.00 to 21.00. Nociceptive sensitivity was determined in the tail-flick test. Control mice were tested for 50 h. The number of tests was 10-11 with intervals of 2.5-8.5 h. To study the role of cerebral hemispheres, 2-3 days prior to experiment the mice were operated under ether narcosis. Soft tissues were removed in the frontoparietal region and the bilateral trepanation entry holes 1 mm in diameter were drilled. The experiment lasted about 30 h and included 5 series with 5-min intervals within a series. In the first mouse the layer of regenerated

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epithelium was removed (sham operation). After a similar preparatory procedure, a piece of filter paper sucked in 25% KCl was applied to the left trepanation orifice of the second mouse to induce spread depression (inactivation) of the corresponding hemisphere [8]. The third mouse was subjected to similar procedure via the right trepanation orifice. The nociceptive sensitivity was assessed 15 min postoperation. Each mouse was tested only one time. The data were processed by spectral analysis for nonequidistant samples. The periodogram plots revealed rhythmic oscillations. The parameters of this oscillations and the corresponding confident intervals were calculated and the true course of the oscillatory curve was approximated [2,3]. Since the determined parameter was latency of reaction, the acrophase of the rhythm corresponded to the minimum of nociceptive sensitivity.

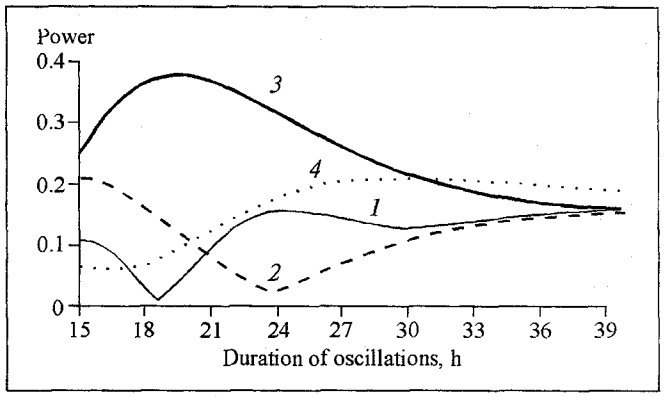

Fig. 1. Circadian periodograms of nociceptive sensitivity in mice with unilateral inactivation of cerebral hemispheres. Here and in Figs. 2 and 3: *1*) intact mice; *2*) sham-operated mice; *3*) left hemisphere is inactivated, right hemisphere is active; *4*) right hemisphere is inactivated, left hemisphere is active.

RESULTS

Statistically significant ($p<0.05$) peaks in periodogram with oscillation periods of 24 and 12 h were revealed in intact mice (Fig. 1, *1*; Table 1). The acrophase occurring in daytime (3.7±0.5 rad) corresponds to 14±2 h. Variation of the parameters of nonlinear approximation showed that the optimal shape of circadian oscillations in intact animals (Fig. 2, *1*) is extremely close by duration to that of day (24.2 h); the signal power increases from 0.024 to 0.044 compared with the sinusoidal waveform. The wave of the true course of diurnal cycle peaked at about 16.00-17.00. More detailed mathematical smoothing (with a window less than 24 h) revealed two waves that were superimposed on the basic wave. They reflect ultradian (12 h) oscillations of nociceptive sensitivity (Fig. 3, *a, 1*). This superposition of waves resulted in a decrease of nociceptive sensitivity two times a day: at about 9.00-10.00 and 18.00-20.00.

There was no circadian component in the spectrum of sham operated mice (Fig. 1, *2*). However, the amplitude and power of the 12-h component was enhanced in these mice (Table 1). Approximation of the true course of the curve did not reveal circadian changes (Fig. 2, *2*). Taking into account the ultradian oscillations, two basic waves were revealed, which coincided in phase with elevations of the similar curve in intact mice but had much greater amplitudes (Fig. 3, *a, 2*). Therefore, sham operation of mice with retained activity of both hemispheres suppressed circadian rhythm and increased the amplitude of ultradian oscillations which had similar structure with the initial ones.

After inactivation of LCH (i.e., under unilateral activity of RCH) circadian acrophase was shifted to the ultradian boundary: to 20 h (Fig. 1, *3*). The amplitude, power, and probability of this rhythmical component greatly increased in comparison with those in intact mice (Table 1). An essential feature

TABLE 1. Circadian Rhythms of Nociceptive Sensitivity in Mice with Unilateral Cerebral Hemisphere Inactivation (*M±m*)

Group	Period of oscillations, h	Amplitude, sec	Acrophase, rad	Power	Probability (1-P)	Mean, sec
Intact (n=12)	24.7*, -5.0	0.43±0.23	3.66±0.50	0.024	0.955	7.39±0.16
	11.9, +5.0, -1.4	0.51±0.23	4.81±0.43	0.040	0.985	
Sham operated (n=59)	Circadian periodicity is absent					8.10±0.58
	11.8*, -1.8	1.41±0.68	3.95±0.45	0.069	0.970	
Inactivation of LCH (n=59)	19.6*, -9.8	2.62±0.85	1.05±0.31	0.131	0.992	9.02±0.69
	11.4*, -1.9	2.36±0.83	1.70±0.34	0.098	0.985	
Inactivation of RCH (n=59)	29.4*, -16.9	1.46±0.93	3.226±0.57	0.042	0.932	8.58±0.62
	6.3**, +1.2	1.57±0.92	3.88±0.53	0.057	0.958	

Note. The upper (*) and lower (**) boundaries of the confident interval are indeterminate.

is confinement of the acrophase to the middle of the dark phase of the day (1.1±0.3 rad at this period length corresponds to 3.5±1.0 h), which attests to inversion of circadian rhythm of nociceptive sensitivity in this group in comparison with intact animals. Approximation of the true course of the curve yielded a more precise duration of oscillation period (23.3 h) and corroborated the inverse character of rhythmicity: the sensitivity was decreased at 4.00-6.00. (Fig. 2, *3*). The 12 h oscillations were also inverted relative to the control (Table 1, Fig. 3, *b*). Thus, under isolated activity of RCH, the ultradian and circadian components of nociceptive sensitivity were not only retained, but augmented, although their phases were inverted in comparison with intact mice.

In the mice with isolated activity of LCH (and with inactivated RCH) the wide and flat rise of the periodogram was shifted to the boundary of infradian range (Fig. 1, *4*). The parameters of this rhythm are given in Table 1. Circadian periodicity has wide confident boundaries and low probability of existence, although the power and amplitude of oscillations increased against the control level. Taking into account the shape of oscillations, the period was determined as 26.2 h, which is similar to that in intact mice (Fig. 2, *4*). As in intact mice, the minimal nociceptive sensitivity was observed in the middle of the light phase of a day. Ultradian oscillations had higher frequency than in other groups (Table 1, Fig. 3, *c*). Thus, in mice with isolated activity of LCH circadian periodicity was less expressed than in mice with active RCH. The spectrum of ultradian oscillations in these mice is changed, but as in intact mice, the minimal nociceptive sensitivity was observed in the middle of the light phase of day. Unilateral inactivation of cerebral hemispheres did not affect the mesor of the rhythms (Table 1), which shows that taken alone the mean diurnal values of nociceptive sensitivity could not reveal the regulatory role of cerebral hemispheres.

Therefore, cerebral cortex plays a key role in regulation of rhythmicity of nociceptive sensitivity in mice. This regulation is characterized by different influences of LCH and RCH, i.e., by interhemisphere asymmetry. Intact mice have the circadian rhythm of nociceptive sensitivity with a minimum in the middle of daytime as well as a 12-h periodicity. Inversion of the rhythm phase after inactivation of LCH and the maintenance of phasic relationships after inactivation of RCH imply the existence of two circadian oscillators that can be designated as "daytime" (direct) and "nocturnal" (inverted) and that regulate the daily rhythmicity of nociceptive sensitivity. A similar hypothesis was advanced earlier for a leading circadian oscillator [7]. Evidently, 12-h

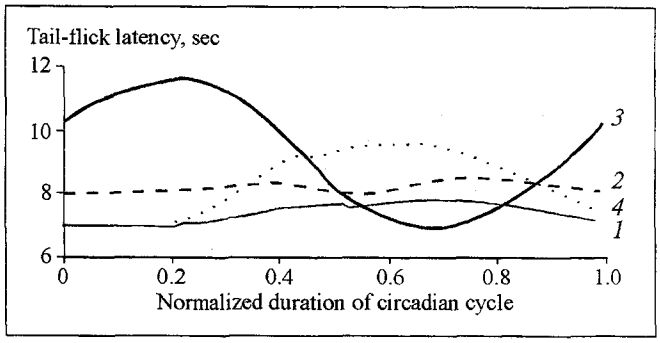

Fig. 2. The course of circadian oscillations of nociceptive sensitivity in mice with unilateral cerebral hemisphere inactivation.

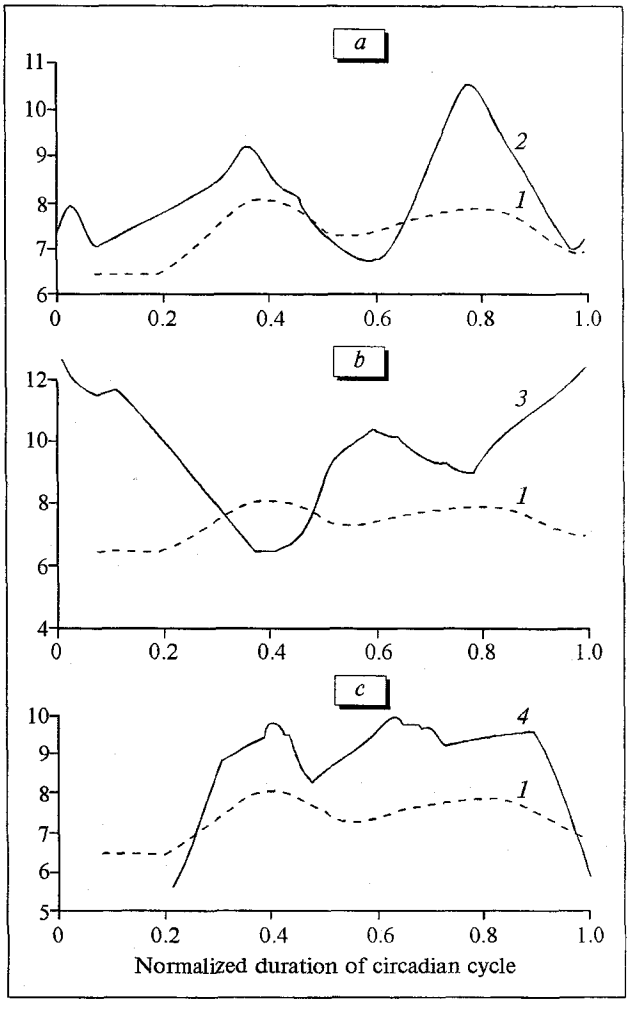

Fig. 3. The course of circadian oscillations of nociceptive sensitivity in mice with regard to the ultradian components. Ordinates: tail-flick latency, sec.

oscillations are controlled in a similar way by two oscillators (direct and inverted). Daily (direct) circadian and direct ultradian oscillators dominate in intact mice. Selective inactivation of cerebral hemispheres showed that the activity of dominating daily oscillator is maintained or synchronized by LCH, while RCH plays a similar role for the inverted

oscillator. In addition, each hemisphere produces an inhibitory effect on the contralateral hemisphere.

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