Effect of Noolit, a Novel Lithium Preparation, on Electrophysiological Activity of Rat Cerebral Cortex

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The effects of lithium carbonate and Noolit, a novel lithium enterosorbent, on electrophysiological activity of cerebral cortex in rats were compared. Both agents potentiated the θ-, α-, and β-rhythms and modified the response to rhythmic flash stimulation from potentiation to inhibition of cerebral rhythms. Moreover, these drugs increased dispersion of all rhythms. By contrast to lithium carbonate, the effect of Noolit was milder and developed more slowly.

Key Words: *Noolit; enterosorbent; lithium; electrophysiology; cerebral cortex; cerebral rhythms*

Lithium preparations produce a normothymic effect, which is responsible for normalization of pathologic activation or inhibition of affective activity to a conventional mean level [1]. However, side effects related to pronounced pharmacokinetic instability of lithium concentration considerably impede clinical use of these preparations [6]. This problem can be solved by synthesis of prolonged lithium preparations. It is known that therapeutic activity of lithium salts is manifested by changes in δ-, γ-, and α-rhythm power [5]. At the same time, EEG parameters can serve as the markers of both therapeutic and toxic activity of lithium salts [4].

Our aim was to compare the effects of lithium carbonate and enterosorbent Noolit (lithium preparation with prolonged action) on electrophysiological activity in rat cerebral cortex.

MATERIALS AND METHODS

The study was carried out on 24 male outbred rats weighing 250-280 g. Conventional certified rats were obtained from Biomodel Department of Tomsk Research Center. The animals were subdivided into 3 groups (8 animals each). Group 1 rats received Noolit (Institute of Experimental and Clinical Lymphology, Siberian Division of the Russian Academy of Medical Sciences, Nov' Scientific-and-Production Company) in a dose of 665 mg/kg. Group 2 rats received 9 mg/kg lithium carbonate (ICN Oktyabr' JSC), which was equivalent to Noolit by lithium content. Control rats received water. The agents were suspended in distilled water and given once daily for 5 days (through a gastric tube).

Electrical activity of cerebral cortex was recorded three times: before application of the drugs (baseline data) and on days 2 and 5 of treatment. The electrodes were implanted into visual cortex (AP=+5, L=2, H=1.5). The indifferent electrode was attached to nasal bones. EEG was regorded using an Era-9 electroencephalograph. The data were analyzed on OTE Biomedica Berg-Fourier analyzer. The epoch length in power spectrum analysis was 248 sec. The rhythms were analyzed in the following frequency ranges: 0.5-4.0 Hz (δ-range), 4-8 (θ-range), 8-13 (α-range), 13-22 (β_1-range), and 22-32 (β_2-range) [2]. The spectrum power data were characterized by the following spectrum coefficients: K_1, the power ratio of θ/δ-rhythms; K_2, the power ratio of θ/α-rhythms; and K_3, the ratio of δ-rhythm power to total power of α-, β_1-, and β_2-

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rhythms. Seven successive recording sessions were performed in a day: before (3 sessions, resting conditions), during (1 session), and after (3 sessions) flash stimulation (7 Hz for 5 min), respectively. Responses were assessed by averaging the first 3 measurements (at rest) and by changes in the power in response to flash stimulation. In addition, 7 experimental values of the same parameters recorded during one day were used to calculate the standard deviation, which characterized power dispersion in percentage of the mean value of this parameter obtained in 3 baseline (resting) measurements in the examination day. The data were processed statistically using Fisher parametrical test and non-parametrical Wilcoxon's test [3].

RESULTS

Under resting conditions, in control rats only θ-rhythm power decreased with time. Both Noolit and lithium carbonate decreased the power of δ-rhythm on day 2. However, at this term lithium carbonate demonstrated a tendency to increase the power of all other rhythms, while Noolit decreased these values insignificantly. On day 5, both agents increased power of all rhythms, and this rise was more pronounced in rats receiving lithium carbonate. The tested substances produced no significant changes of spectrum coefficients (Table 1).

In control rats, flash stimulation insignificantly increased power spectrum in all frequency ranges except δ-rhythm (Table 2). In rats receiving lithium carbonate this stimulation significantly decreased all rhythms on day 2, and this decrease became more pronounced on day 5, especially in θ-range. By contrast, in Noolit-treated rats flash stimulation increased power spectrum in all frequency ranges on day 2 (especially in δ- and θ-ranges). On day 5, spectrum power decreased in all frequency ranges, especially in δ-range. However, this decrease in spectrum power in θ-, α-, and β-frequency ranges was less pronounced than in rats treated with lithium carbonate.

On day 2, lithium carbonate increased all spectrum coefficients and dispersion of spectrum power, especially in α-, β_1-, and β_2-ranges (Table 3). These changes became more pronounced on day 5. In rats treated with Noolit dispersion of power spectrum parameters was observed only on day 5, and it was 2-2.5 times less pronounced than that induced by lithium carbonate. Noolit had no effect on spectrum coefficients K_1, K_2, and K_3.

Both examined agents produced similar changes in electrical activity of the brain. However, changes produced by Noolit were less pronounced and delayed by 2-3 days in comparison with those produced by lithium carbonate. In addition, in rats receiving Noolit we observed less pronounced variations in cerebral

TABLE 1. Effect of Lithium Carbonate and Noolit on Power Spectrum of Electrical Activity in Rat Visual Cortex (mV^2/Hz, *M±m*)

Parameter	Control			Lithium carbonate (9.1 mg/kg)			Noolit (665 mg/kg)		
	baseline	day 2	day 5	baseline	day 2	day 5	baseline	day 2	day 5
δ-rhythm	35.2±6.7	30.9±4.0	27.1±3.3	29.3±5.9	20.9±0.5	53.4±4.5^{*+}	41.0±6.5	17.8±3.2^{*+}	58.7±10.2$^{*\circ}$
θ-rhythm	16.2±1.0	13.9±0.9	10.5±1.1*	15.6±0.9	20.6±3.7	41.7±7.4^{*+}	16.9±1.1	12.8±1.4	28.9±6.9^{+}
α-rhythm	5.4±0.5	6.5±1.2	5.8±0.7	5.8±0.6	13.3±3.3	19.7±4.5^{*+}	5.0±0.5	3.1±0.3^{*+}	8.2±2.5
β_1-rhythm	1.8±0.5	2.2±0.5	2.0±0.5	2.2±0.5	4.1±0.2^{*+}	8.1±2.1^{*+}	1.3±0.4	1.0±0.2	1.8±0.7
β_2-rhythm	0.2±0.12	0.24±0.14	0.22±0.15	0.3±0.1	0.5±0.1	1.1±0.3^{*+}	0.1±0.1	0.4±0.2	0.12±0.05
Total power	58.7±6.9	53.7±5.0	45.6±4.9	53.2±6.0	59.3±5.5	123.9±18.8^{*+}	64.2±7.0	35.3±5.1^{*+}	97.6±14.3$^{*\circ}$
K_1	2.1±0.3	2.3±0.5	2.4±0.5	1.8±0.2	1.2±0.2	1.5±0.2	2.4±0.3	1.5±0.2*	2.2±0.2°
K_2	3.2±0.3	3.6±0.4	3.3±0.4	2.8±0.4	1.8±0.2*	2.5±0.3	3.5±0.3	4.1±0.3	3.9±0.2
K_3	5.8±1.5	3.6±0.9	4.1±0.7	4.4±1.3	1.6±0.4	2.9±0.9	7.2±1.4	4.6±0.7	7.8±1.2

Note. Here and in Tables 2, 3: $p<0.05$ *compared to baseline, $^{+}$compared to the corresponding parameter in control rats, $^{\circ}$compared to corresponding parameter on day 2.

TABLE 2. Effect of Rhythmic Flash Stimulation on Power Spectrum of Electrical Activity in Visual Cortex of Control and Experimental Rats (mV^2/Hz, *M*±*m*)

Frequency range	Control			Lithium carbonate (9.1 mg/kg)			Noolit (665 mg/kg)		
	baseline	day 2	day 5	baseline	day 2	day 5	baseline	day 2	day 5
δ-rhythm	+2.0±7.4	-1.1±0.4	-0.2±0.5	+5.7±8.0	-12.4±2.1^{+}	-15.4±22.7	-1.8±6.3	+10.8±1.4^{+}	-24.3±3.6^{*+o}
θ-rhythm	+1.2±3.7	+0.3±0.5	+1.3±1.0	+3.4±3.9	-13±4.5^{*+}	-23.7±15.6	-1.0±3.2	+8.6±3.4^{+}	-4.7±1.3^{+o}
α-rhythm	+0.7±1.4	+0.5±0.3	+0.2±0.2	+1.6±1.5	-10.1±3.7^{*+}	-14.3±7.1	-0.3±1.2	+0.5±0.2	-0.7±0.2^{+o}
β_1-rhythm	+1.1±0.8	+0.4±0.2	+0.3±0.2	+1.8±0.9	-2.7±0.9^{*+}	-7.0±2.8^{*+}	+0.5±0.7	+0.7±0.08	+0.2±0.3
β_2-rhythm	+0.16±0.09	+0.2±0.1	+0.03±0.04	+0.24±0.1	-0.4±0.1^{*+}	-1.0±0.4*	+0.09±0.07	+0.2±0.1	-0.03±0.01

TABLE 3. Effect of Lithium Carbonate and Noolit on Dispersion of Power Spectrum of Electrical Activity in Rat Visual Cortex (%, *M*±*m*)

Parameter	Control			Lithium carbonate (9.1 mg/kg)			Noolit (665 mg/kg)		
	baseline	day 2	day 5	baseline	day 2	day 5	baseline	day 2	day 5
δ-rhythm	20.3±2.8	26.8±7.9	18.4±3.8	21.7±2.5	76.9±15.3^{*+}	73.4±6.4^{*+}	18.9±2.9	39.5±6.0*	46.3±7.4^{*+}
θ-rhythm	24.4±4.9	31.4±4.9	29.3±8.2	25.0±4.9	76.9±13.9^{*+}	96.2±3.4^{*+}	23.8±4.9	36.8±1.7	54.1±4.8^{*+o}
α-rhythm	28.2±9.5	31.6±8.2	20.9±3.5	31.9±8.7	87.9±13.6^{*+}	121.0±9.9^{*+}	24.5±10.0	32.0±7.3	42.6±4.9^{+}
β_1-rhythm	33.4±9.1	21.1±6.8	18.9±2.3	35.7±8.7	76.9±10.0^{*+}	126.7±7.9^{*+}	31.1±9.4	19.1±3.3	58.7±11.3^{*o}
β_2-rhythm	15.6±3.5	13.1±8.3	27.0±13.7	8.4±3.7	106.4±11.5^{*+}	133.7±13.8^{*+}	17.8±2.8	16.5±7.4	27.2±12.2
Total power	20.9±4.3	16.9±3.2	16.4±3.5	22.6±4.2	78.5±14.4^{*+}	95.4±3.9^{*+}	19.3±4.3	37.0±3.3^{*+o}	47.9±6.7*
K_1	16.1±2.7	29.2±4.2*	32.8±10.7	16.1±2.7	18.2±1.9	45.8±16.9*	16.1±2.7	19.4±1.0	19.5±6.1
K_2	16.2±4.7	53.9±19.0	29.9±6.7	14.5±5.0	29.3±3.7^{*+}	73.2±11.7*	17.9±4.2	28.8±3.4	17.0±1.4
K_3	19.8±6.8	59.4±17.7	26.7±6.0	20.6±6.6	36.0±8.9	151.6±22.6^{*+}	19.1±7.1	34.3±6.9	16.4±2.2

electrical activity and did not found disturbances in proportions between various ranges of spectrum power.

Thus, lithium carbonate and Noolit increased power of rhythmic electrical activity in rat cerebral cortex, which was most pronounced in θ-, α-, and β-frequency ranges. Both agents decreased power and increased dispersion in all frequency ranges recorded during repetitive flash stimulation. In contrast to lithium carbonate, Noolit is characterized by milder action, delayed effects, less pronounced destabilization influences on electrical activity of the brain; normal response to flash stimulation was disturbed to a lesser extent.

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