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Delayed Motor Stereotypies and Psychoaffective Disorders in Rats Evoked by Rhythmic Electrical Stimulation of the Right Sensorimotor Cortex

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Persistent behavioral and postural changes were detected in rats 4-5 days after rhythmic electrical stimulation of the right sensorimotor cortex, which evoked anxiety, aggressive behavior, and fear. Characteristic motor disorders were the manege moving, whose direction correlated with the turn of the head, retropulsions, rhythmic upward jerks of the head (tics), and orofacial dyskinesia (sniffing, mastication, and gnawing). These symptoms rose during 2-3 weeks and then attenuated albeit being retained in a weakened form throughout the entire (up to one year) observation period. The possible mechanisms of genesis of the delayed behavioral disorders and other neuropathophysiological syndromes evoked by rhythmic electrical stimulation of the sensorimotor cortex are discussed.

Key Words: *sensorimotor cortical hyperactivity; motor stereotypies; psychoaffective disorders; delayed excitotoxic neurodegeneration*

Hyperactivation of a given region in the nervous system can induce long-lasting structural and functional changes both in the stimulation focus and in the related brain structures [2,5,8,9,16]. Previously, we demonstrated that rhythmic electrical stimulation (RES) of the sensorimotor cortex (SMC) induces formation of generator of pathologically enhanced excitation in SMC; after the end of RES the processes continued developing, which 1 day later led to an increase in the number of neurons involved in generation of the seizure tail discharge [3,4]. It can be supposed that RES of SMC may elicit some other delayed pathological phenomena as well. To check up this hypothesis, the behavior of animals was observed at different periods after RES.

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MATERIALS AND METHODS

The study was carried out on male albino rats weighing 250-300 g. RES of a fragment of the right hemisphere SMC was performed via undamaged dura mater using low frequency pulse trains (8 Hz, train duration 10 sec, interval between trains 10 min). The method of current strength selection to obtain the tail discharge with stable parameters and the specialties in positioning of the stimulating and recording electrodes were described elsewhere [3,4]. On the first experimental day, 20 trains of electrical pulses were applied, followed by additional 5 trains on the next day. Control animals were subjected to the same procedures: they were operated, immobilized with curare, artificially ventilated, and put into the restraining apparatus, with electrodes located on the brain surface in the same way as in the experiments with

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RES. After suturing of the wound, the rats were maintained in vivarium. The behavior of rats was examined at least once every day within the first 3-4 weeks after RES, and about once a week during the following 2-12 months. Motor activity was assessed in an Orto-Varimex (Columbus Instruments) apparatus. The results were statistically analyzed using Student's *t* test.

RESULTS

The behavior of control rats (operated, immobilized with curare, artificially ventilated in the restraining apparatus, and with electrodes located on the brain) did not differ from the behavior of intact rats (Table 1). Postural and behavioral changes (Table 1) appeared 4-5 days after the second procedure of RES. During the following 1-2 weeks the intensity of symptoms increased and then decreased (Fig. 1). The symptoms were retained during the entire observation period (about a year). Hairiness of rats was observed at the end of the year.

Experimental rats demonstrated drastic psychoaffective disorders. Anxiety was caused by experimenter's approaching, which was expressed in chaotic runs in the cage. By contrast to control animals, exploring motor activity of these rats in the open field test did not increased during 4 weeks (Fig. 2). In addition to horizontal activity, the high anxiety level of stimulated rats was manifested by drastic increase in the number of sets (20.7±5.2 during 5 min). Some rats in experimental group (Table 1) feared the approaching of experimenter's hand: they tried to press to floor and loudly vocalized for a long period. Shaking of the cage floor or strong sound provoked all the stimulated rats to rise and assume the defensive posture. The defensive posture and persistent vocalization were observed for several minutes, thereafter the rats fell on the back, jerked convulsively and came to a standstill in supine position. After 0.5-1.0 min, the behavior of the rats returned to that observed before stimulation. To this time (1-2 weeks poststimulation) the snouts were bitten and even markedly gnawed in some rats.

Sustained changes in muscle tone were observed in cervical muscles, which led to spastic torticollis

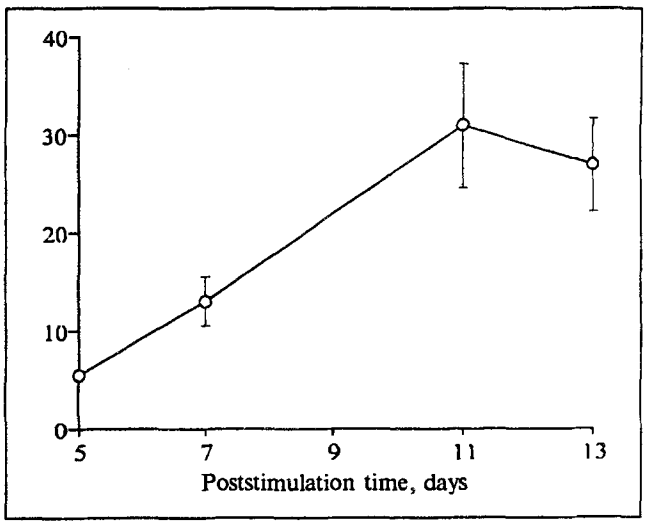

Fig. 1. Changes in stereotype head upward jerks appearing in rats after two series of RES of SMC. Ordinate: number of head jerks during 5 (n=6).

(Table 1). At the same time, there was a regular phasic muscle activation manifested by repeated upward jerks of the head (Table 1, Fig. 1). Another form of motor automatism, the manege moving, appeared even more frequently (Table 1). It occurred in counter- and clockwise direction. The predominant direction of the turns usually corresponded to the head turn (Table 2). All 9 rats of this group made regular upward jerks of the head (the rate of jerks was 44.8±4.6 for 5 min).

In addition to rotation, the stimulated rats demonstrated coordinate backward movements, retropulsions (Table 1), orofacial stereotypies (sniffing, mastication, and gnawing) as well as sexual grooming. As a rule, the orofacial stereotypies were the earliest (1-2 days) behavioral changes after RES.

Thus local RES of SMC evoked different motor and psychoaffective disorders (Table 1). According to the theory of generator, determinant, and system mechanisms of neuropathological syndromes [1,2, 11], every syndrome is based on a pathological system formed by pathological determinant. In our experiments the primary pathological determinant is a hyperactive region of SMC [3,4]. Recruiting another cerebral structures into this process, this determinant

TABLE 1. Syndromes Appearing in Rats Subjected to Local RES of a Region in SMC

Type of stimulation	Phasic upward jerks of the head	Retropulsions	Spastic torticollis	Fear	Head-to-tail turning
	percentage of rats in the group				
Repeated RES (n=45)	45	33	42	9	60
Control (n=44)	0	0	0	0	0

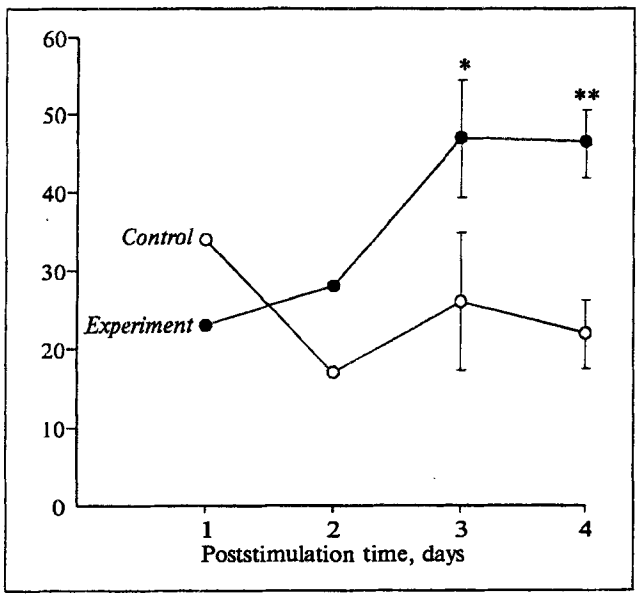

Fig. 2. Changes in motor activity in rats after RES of SMC (open field test, n=6). Ordinate: the number of squares crossed for 3 min. *p<0.05, **p<0.02 in comparison with the control group.

raises secondary determinants, which trigger of the pathological systems of these syndromes.

According to symptoms, pathological systems of various syndromes appear at different periods after RES and are retained for a long time. Symptomatic analysis of the syndromes attests to various complicated neuropathophysiological and neurochemical mechanisms of formation of these pathological systems, which include a long-term activation of neurons, elimination of controlling influences, and plastic rearrangements.

One of the consequences of hyperactivation of SMC are the stereotypic motor disorders (Table 1). These disorders are qualitatively different from the contralateral phasic muscle jerks, which were observed during recording of seizure discharges in SMC, and from generalized seizures caused by classical kindling of limbic structures [8]. Behavioral effects of chemical activation of the anterodorsal striatum [7,10] into which the corticofugal SMC neurons are projected [14] points to a possible participation of this structure in realization of poststimulatory behavioral stereotypies in which it operates as a link of the pathological system. Locomotor hyperactivity (Fig. 2), rhythmic movements of the head (Fig. 1), orofacial dyskinesia (sniffing, mastication, and gnawing) can be elicited by disturbances in GABAergic inhibition in the head of the caudate nucleus [1]. The psychoaffective phenomena (fear and aggressive behavior) observed in rats subjected to RES of SMC do not occur when the striatum is chemically stimulated [1]. Together with locomotor activation they may be caused by activation of some structures of the limbic-motor loop [6,16].

One can suppose that behavioral stereotypies after RES are caused by excitotoxic damage to the SMC and striatum neurons. In fact, after mechanical damage to SMC locomotor hyperactivity and stereotypic behavior caused by dopaminergic activation are augmented, which attests to the inhibitory influence of SMC on their generation [6]. The same effect is observed after the excitotoxic damage to the striatum [5].

The hypothesis on an excitotoxic damage to cerebral neurons caused by RES of the SMC agrees with the observation that excitotoxic damage to neurons located in the hyperactivity focus and in the projection zones of hyperactive neurons occurs during few hours [13,16]. Increase in the thresholds of the direct response and a drastic increment of the focal seizure potential amplitudes in the stimulated region of SMC have been observed on the next day after RES [4]. In the classical kindling of limbic structures, such changes in electrical responses are induced by selective degeneration of excitatory and inhibitory neurons [15].

Disappearance of some proteins in SMC and ipsilateral striatum was observed in stimulated rats with developed stereotypic syndrome, which may indicate the death of the corresponding synthesizing neurons. Behavioral disorders were developed in rats during 2-3 weeks after RES (Fig. 1 and 2), i.e., when neuronal degeneration leads to morphofunctional rearrangements in the neural network, denervation hypersensitivity, sprouting of the nerve fibers, and reactive synaptogenesis [16]. It is noteworthy that the locomotor hyperactivity caused by excitotoxic damage to the prefrontal cortex in rats and by the concurrent denervation in *n. accumbens* [9] appears with

TABLE 2. Direction and Number of Turns in Rats with Fixed Turn of the Head ($M \pm m$)

Group		n	Number of turns for 5 min	
			to the right	to the left
Head is turned	to the right	5	39.6±16.5	4.3±1.3
	to the left	3	4.2±1.4	18.2±9.3
Control animals		10	0	0

the same large latency and develops at the same slow rate as delayed behavioral disturbances in our experiments (Figs. 1, and 2).

Muscle rigidity causing a tilt of the head and the manege moving (Table 1) may be induced by weakening of the nigrostriatum projections. Damage to SMC can provoke morphological changes in *s. nigra*, similar to those observed in the brain of parkinsonian patients [12].

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