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Effects of Electrical Stimulation of the Cerebellum and Injections of Levetiracetam on Aggressive Behavior of Kindling Rats

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In rats with the corazole-induced kindling syndrome, we estimated the conditions for the appearance of battles on an electrified floor; the threshold for initiation of aggressive reactions in kindling animals was lower, on average, by 41.5%, as compared with the corresponding index in intact animals. Combination of electrical stimulation (ES) of the paleocerebellar cortex (lobules V-VII; 100 sec^{-1}; altogether 10 sessions of ES) and injection of levetiracetam (40.0 mg/kg, i.p.), which *per se* did not influence significantly aggressive behavior of kindling rats, led to an increase in the threshold for the appearance of battles, on average, by 28.8% ($P < 0.05$), compared with the initial value in the tested animals, i.e., to a drop in the level of aggressiveness.

Keywords: chemical kindling, aggressive behavior, electrical stimulation (ES) of the cerebellum, levetiracetam.

INTRODUCTION

Aggressive behavior of animals is intensified under conditions of formation of kindling, a model of the epileptic syndrome [1, 2]. This is, in particular, manifested in a decrease in the threshold for the appearance of battles between animals under conditions of testing their pairs in an experimental chamber equipped with an electrified floor [2]. Transcranial magnetic stimulation of the brain is capable of decreasing behavioral aggressiveness, which can be related to activation of cerebral structures belonging to the antiepileptic system [2, 3].

In our study, we examined the effect of electrical stimulation (ES) of the cerebellar archeocortex on manifestations of aggressive behavior of intact rats and animals with pharmacological kindling. In addition, we studied indices of aggressive behavior under conditions of combined application of ES and injections of levetiracetam. The action of the latter differs from that of other antiepileptic drugs (in particular, this agent does not suppress the cognitive functions). In different forms of epilepsy, the spectrum of the use of levetiracetam varies within a wide range [4].

METHODS

Under Nembutal anesthesia (40.0 mg/kg, i.p.), bipolar Nichrome electrodes (interelectrode distance 0.25-0.3 mm) were implanted in lobules V-VII of the paleocerebellar cortex of male Wistar rats (body mass 170-240 g). The electrodes were fixed to the surface of the skull using Noracryl plastic. Behavior of the rats was observed beginning from the 7th to10th day from the moment of implantation.

Kindling in rats was formed according to the described technique [2] using daily i.p. injections of corazole in a dose that was subthreshold for the development of convulsions (25.0 mg/kg). In experiments, we used only rats demonstrating generalized seizure phenomena during the last 3 days of the period of injections of the epileptogenic agent. Rats of the control group were injected with physiological saline using an analogous protocol.

The aggressiveness of animals was studied in rats placed in a chamber (25 × 45 × 30 cm) with an electrified floor [2]. On the 10th to 15th sec, limbs of the animals were subjected to electrical stimulation with an initial intensity of 0.2 mA. The current intensity was slowly increased up to the

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appearance of clearly pronounced manifestations of aggressive behavior (beginning of battles).

For ES of the cerebellar cortex, we used rectangular current pulses (50-100 μA) with a frequency of 100 sec^{-1}. Episodes of ES lasted 2.5 sec; intervals between episodes were 2.5 to 3.5 min long. Levetiracetam (USB Pharma, Belgium) was used i.p. in doses of 40.0 or 80.0 mg/kg 10 min prior to ES. In the control group, rats were injected with saline instead of levetiracetam and underwent all manipulations related to ES but without stimulation *per se*.

After termination of the observation period, the animals were euthanized and decapitated; localization of electrodes in the cerebellar cortex was controlled on frontal slices.

For statistical processing of the numerical data, we used dispersion analysis (ANOVA) and the Newman–Keuls test.

RESULTS

The threshold for initiation of the battles under nociceptive stimulation of the limbs in control sham-operated rats was, on average, 1.7 ± 0.2 mA. In the case where we used 20 sessions of ES of the paleocerebellar cortex in rats of the control group, the threshold for manifestations of aggressiveness (battles) became somewhat higher (by 5.7%; $P > 0.05$). A more considerable (but also insignificant) increase (by 11.4%, $P > 0.05$) was observed under conditions of 10 ES sessions made in a parallel manner with the use of i.p. injections of 40.0 mg/kg levetiracetam (not illustrated).

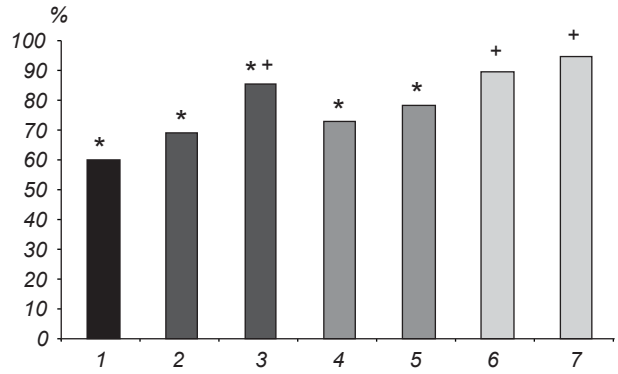

Fig. 1. Normalized values (%) of the thresholds for the appearance of aggressive behavior in pairs of rats under conditions of electrical stimulation (ES) applied to the cerebellum and under the action of levetiracetam. Horizontal scale, 1) kindling rats; 2 and 3) 10 and 20 sessions of ES applied to the cerebellar cortex, respectively, 4, 5) after injections of levetiracetam (40 and 80.0 mg/kg, respectively), and 6 and 7) 10 sessions + levetiracetam (40 and 80 mg/kg, respectively); the mean threshold for aggressive reactions in intact rats (control) is taken as 100%. $^{*}P < 0.05$ with respect to the index in the group of kindling rats with no stimulation and action of levetiracetam.

In rats with the formed kindling, the threshold for the appearance of battles on the electrified floor was, on average, 1.0 ± 0.1 mA, i.e., it was significantly lower, as compared with the index in intact rats (by 41.5%; $P < 0.05$; Fig. 1, 1). After 10 sessions of ES of the paleocerebellar cortex, the studied index increased but remained lower, as compared with that in the group of intact (sham-operated) rats by 32.8% ($P < 0.05$; Fig. 1, 2). The threshold for the appearance of battles in kindling rats after 20 ES sessions of the paleocerebellar cortex was smaller than that in intact rats by 16.4% ($P < 0.05$) but exceeded the threshold for battles in kindling rats by 25.1% ($P < 0.05$; Fig. 1, 3).

In the case where we used levetiracetam (40.0 mg/kg, i.p.), the examined index remained lower than in the control group (in sham-operated rats) by 28.9 % ($P < 0.05$), while in the case of the use of a two times greater dose, such index remained lower by 23.7% ($P < 0.05$; Fig. 1, 4, 5). At the same time, certain suppression of aggressiveness, as compared with that in kindling rats with no introductions of this agent, was obvious.

Against the background of injections of levetiracetam (40.0 mg/kg) and ES (10 sessions) of the paleocerebelalr cortex, the threshold for the appearance of battles remained smaller than in the control group by 12.7% ($P > 0.05$), but at the same time, it significantly (by 28.8%, $P < 0.05$) exceeded the corresponding index in kindling rats (estimated at the maximum of formation of the kindling syndrome; Fig. 1, 6). In the case where we used levetiracetam in a higher dose (80.0 mg/kg) and performed 10 sessions of ES of the cerebellar cortex, the threshold for the appearance of aggressive reactions returned nearly to the control values and was lower than that in control rats by only 7.6% ($P > 0.05$); it exceeded the initial value in kindling rats by 33.9% ($P < 0.05$; Fig. 1, 7).

DISCUSSION

Therefore, the above-presented data indicate that the use of ES applied to the paleocerebellar cortex of rats subjected to the procedure of kindling leads to certain suppression of aggressive behavior of animals, which was estimated from the value of

threshold for the development of battles in pairs of animals on the electrified floor. This effect of ES applied to the paleocerebellum is intensified in combination with the action of levetiracetam. The mechanism underlying realization of such influence of the paleocerebellum can be explained by the involvement of the cerebellar structures in the formation of affective disorders, cognitive dysfunctions, and the development of depression [1, 5]. Atrophy of the cerebellar archeocortex in humans promotes aggressiveness of patients and also intensifies the development of depression [5]. In this context, it should be noted that a rise in the density of alpha-2-adrenoceptors in the cerebellar cortex of patients suffering from Alzheimer's disease correlates with their increased aggressiveness [6].

At the same time, intensification of aggressive behavior is a complication observed under conditions of treatment with levetiracetam [4]. It should be emphasized that the formation of aggressive behavior in kindling rats is related to activation of dopaminergic cerebral mechanisms [7]. It seems possible that precisely because of the fact that ES of the cerebellum and injections of levetiracetam activate catecholaminergic mechanisms [1, 4], a combined action of these factors provides intensification of corrective effects with respect to manifestations of aggressive behavior.

It should be also noted that both ES of the cerebellum and injections of levetiracetam were not accompanied in intact rats by dramatic changes in the examined indices. At the same time, the effects were significantly more expressed in kindling rats. Such increased sensitivity to the action of certain agents and also of endogenous metabolites is typical of the state of kindling and can be related to the effects of functional deafferentation of the corresponding neuronal pools against the background of a rise in the tone of the inhibitory cerebral systems within the interictal period [1, 2].

Experiments were carried out in accordance with the GLP and the Ethics Committee of the Odessa National Medical University (protocol No. 84 from October 10, 2008).

The authors, T. M. Muratova, V. V. Godovan, L. S. Godlevsky, and E. V. Kobolev, confirm that they have no conflict of interest.

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