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COMPARISON OF EPILEPTIC SYNDROMES INDUCED BY LIMBIC ELECTRICAL STIMULATION (KINDLING) WITH 24-48-HOUR AND 5-MINUTE INTERVALS

O. A. Timofeeva

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A phenomenon of rapid kindling has recently been obtained [2, 4, 9], in which a generalized seizure syndrome develops in animals in the course of a few hours in response to electrical stimulation (ES) of the brain with an interval of 3-5 min, instead of the 24-48-h interval used in classical kindling [7]. The present writer showed [4] that one particular feature of rapid kindling is significant and long-lasting inhibition of the postictal refractory period (PIRP). In the course of classical kindling, simultaneously with progression of epileptic responses, antiepileptic responses also are intensified [8, 12, 13]. PRIP in these animals lasts several times longer than in intact animals [11], but during bilateral ES of the amygdala, PIRP lasts even longer than during unilateral stimulation [10]. The following questions accordingly arise: do epileptic reactions differ in animals subjected to classical kindling, and if so, what is the nature of this difference. The investigation described below was undertaken to study these problems.

EXPERIMENTAL METHOD

Experiments were carried out on 34 chinchilla rabbits weighing 2.5-3 kg. Electrodes (nichrome wire 100 μ in diameter) were implanted bilaterally into the sensomotor and occipital zones of the cortex, dorsal hippocampus, and amygdaloid and caudate nuclei bilaterally 2 weeks before the experiment.

The animals were divided into four groups.

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TABLE 1. Duration of Seizures and Afterdischarges in Rabbits during Hippocampal (group 1) and Amygdaloid (group 3) ES with 24-48-Hour Interval and During Hippocampal (group 2) and Amygdaloid (group 4) ES with 5-Min Interval (M ± m)

Parameters	Group			
	1	2	3	4
Duration of seizures, sec	29±5	47±8	39±2	73±6
	—	83±15	—	98±15
	112±13	115±4	101±8	100±4
	—	116±10	—	126±20

In the animals of group 1 (n = 14) the hippocampus was stimulated (200 μ, 1 msec, 60 Hz, duration of session 12 sec) with an interval of 24-48 h; in the animals of group 2 (n = 11) the hippocampus was stimulated (250 μ, 1 msec, 60 Hz, duration of session 2 sec) with an interval of 5 min; in group 3 (n = 5) the amygdala was stimulated (the same parameters as group 1) with an interval of 24-48 h, and in group 4 (n = 4) the amygdala was stimulated (the same parameters as group 2) with an interval of 5 min.

In groups 1 and 3 the experiment began 24 h after determination of the magnitude of the stimulating current (inducing a weak afterdischarge). The electroencephalogram (EEG) and motor reactions of these animals, loosely fixed in a wooden frame, were recorded for 10 min before and 10 min after ES. They were subjected to this procedure for 2-4 weeks, depending on the rate of development of the kindling syndrome. In the animals of groups 2 and 4 the experiment began 5 min after determination of the threshold level of stimulation. Their EEG and motor responses were recorded continuously for several hours. The duration of the after-discharges (in sec), the time of their appearance after each session of ES (in sec), and the character of spread of IS among the brain structures studied were evaluated. The severity of the seizures was assessed on the basis of their duration (in sec) and on a point scale [4].

The arrangement of the electrodes in the brain was determined histologically.

EXPERIMENTAL RESULTS

In the course of the time interval studied a stable and generalized epileptic syndrome developed in 8 of the 14 rabbits of group 1, in 7 of the 11 rabbits of group 2, and in all animals with amygdaloid kindling. On average 18 ± 1.4 ES with a 24-48-h interval and 53 ± 4.5 ES for a 5-min interval were required for its development, allowing for the number of ES given during identification of the threshold level of stimulation. Under these circumstances 6-point clonicotonic seizures developed in all rabbits with amygdaloid kindling, in two rabbits of group 1, and in three rabbits of group 2. In the remaining rabbits with hippocampal ES, 5-point generalized clonic seizures were formed.

The duration of the seizures in animals with rapid kindling was significantly longer than in animals with classical kindling (Table 1). Resumption of ES in animals of groups 2 and 4, 2-4 weeks after the formation of rapid kindling, was accompanied by further strengthening of the seizure syndrome, manifested as a significant increase in the duration of the seizures. The number of animals with 6-point seizures increased to 5 in group 2. A characteristic feature of this period was maximal inhibition of PIRP. Whereas during rapid kindling; after the first two generalized seizures the average duration of PIRP was 105.0 ± 13.7 min, after 4-5 generalized seizures it was 12.0 ± 1.1 min, and when ES was resumed after 2-4 weeks, it fell to 8.0 ± 0.5 min. The increase in the severity of the seizures and simultaneous progressive shortening of PIRP during rapid kindling are evidence of the interlinking of these processes. According to data in the literature [10, 11] and our own observations, in classical kindling the duration of PIRP measures at least several tens of minutes, whereas in rapid kindling only a few minutes, Consequently, the increase in the duration of the seizures in rapid kindling is disproportionately less than the shortening of PIRP, compared with the same parameters in classical kindling. This is evidence that inhibition of PIRP during rapid kindling is not entirely dependent on inhibition of the antiepileptic reactions. Evidently other mechanisms also play a role in the shortening of PIRP and the rapid recovery of generalized seizure reactions. This phenomenon may perhaps be an effect of receptor reorganization of synaptic transmission [1].

TABLE 2. Interictal Spikes (during 5 min) in Rabbits of Groups 1 and 2 (M ± m)

Seizures	Group of rabbits		
	1 (n=12)	2	
		(n=8)	after 1-3 weeks (n = 7)
Generalized	12±1,4 (n=12)	2±0,4 (n=2)	8±1,6 (n=5)
Nongeneralizd	10±1,4 (n=12)	30±5,5 (n=8)	20±2,3 (n=7)

Legend. n) number of animals.

Two types of IS were recorded in animals with both rapid and classical kindling: nongeneralized, when spikes appeared in one brain structure or in two brain structures at once, and generalized, when IS appeared simultaneously in three and more structures. Significant development of IS took place in animals with hippocampal ES: in 12 of the 14 rabbits of group 1 and in 8 of the 11 rabbits of group 2 (Table 2). Nongeneralized IS developed in all rabbits with spike activity. Their average number was significantly greater in animals with rapid kindling. The number of generalized IS, on the other hand, was significantly greater in animals with classical kindling. Generalized IS developed in all rabbits with spike activity in group 1 and only in two rabbits in group 2. A significant increase in the contribution of generalized IS to total spike activity was observed in animals with rapid kindling only on the resumption of ES after 1-4 weeks. Generalized IS appeared in the animals of group 1 after 4-6 ES, but in the rabbits of group 2 much later; in the course of the first experiment, in the case of unsuccessful kindling and in the period of resumption of ES after 1-3 weeks in the case of successful kindling. The number of structures involved in spike activity was greater in the animals of group 1 (7-8 structures) than in those of group 2 (3-4 structures).

All this is evidence that ES with a 24-48-h interval facilitates generalization of IS in the brain to a greater degree than ES with an interval of 5 min. The degree of generalization of IS in the brain is evidence of the degree of development of secondary epileptic foci. Investigations [3, 5, 6] have shown that the multifocal character of epileptogenesis can lead to inhibition of the seizure syndrome. The greater severity of the seizures in animals with rapid kindling was perhaps linked, as well as with other factors, with the less marked development of secondary epileptic foci in the brain.

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