PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Effects of Electrical Stimulation of the Superior Colliculi on Focal Epileptic Activity in the Cerebral Cortex

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It has been shown that when a generator of pathologically enhanced excitation [1] is set up in deep neuronal layers of the superior colliculi (SC) by microinjections of bicuculline, penicillin, or picrotoxin, acute generalized epileptic activity induced by systemic administration of picrotoxin is inhibited, as are generalized picrotoxin-induced convulsions in kindling animals [4]. Activation of the SC by bicuculline introduced into their deep layers also leads to inhibition of maximal electroshock-induced convulsions [9]. Disinhibition of SC structures results in the production of antiepileptic effects following injection of muscimol into the reticular part of the substantia nigra [11].

In the study described here we examined the effects of electrical stimulation (ES) of the SC on focal epileptic activity induced in the cerebral cortex of rats by local application of a strychnine solution.

MATERIALS AND METHODS

For the study, 42 male Wistar rats 170-230 g in weight were used. The effects from ES of the SC were recorded in Nembutal-anesthetized (35 mg/kg intraperitoneally) animals. Before the tests, soft tissues were removed from the bones of the skullcap, the skull was trephined with a drill, and electrodes for ES were implanted according to stereotaxic coordinates of the rat brain [12]. Bipolar exciting electrodes, made of Nichrome wire 0.15 mm in diameter, were fixed to the skull surface with a fast-hardening paste (Acryloxide). Electrical activity in the neocortex was recorded with silver electrodes in direct contact with the cortex. The indifferent electrode was fixed to the nasal bones. A single epileptic focus was set up by applying a 2×2 mm^2 piece of filter paper moistened with strychnine nitrate solution (0.1% or 1%) to the frontal region of the cerebral cortex. Electrical activity was recorded with a 16-channel electroencephalograph (EEG-16, Hungary). Th SC were stimulated with an ESL-2 electrostimulator (parameters: frequency 100 Hz; amplitude 5 V; stimulus duration 0.25 msec). The interval between stimulations was 2 min. After the tests, the location of the electrodes was verified histologically. The results were treated statistically by analysis of variance and nonparametric methods [7].

RESULTS

The objective of the first series of experiments was to see how high-frequency electrostimulation fol-

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lowed by destruction of the SC would influence the activity of a relatively weak epileptic focus set up by application of a 0.1% strychnine solution to the region of the cerebral cortex contralateral to the SC being stimulated. Approximately 7 to 10 min after strychnine application, spikes of 150-300 μV appeared at the application site and increased up to 500 μV during the next 1-3 min, at which time the firing frequency was 24-40 cpm (Fig. 1, *I*, *a*). Such activity remained stable for 6-12 min after which the spike potentials progressively decreased in amplitude and frequency to disappear altogether over the next 3-7 min. The focus of epileptic activity existed for 10 to 22 min.

Stimulation of the SC during the period when discharges of stable amplitude and frequency were being generated in the epileptic focus (8-13 min after application of the convulsant) led to inhibition of epileptic potentials in 6 of the 7 rats when stimulation was started (Fig. 1, I, *b*). When it was discontinued, spikes reappeared within 5 to 10 sec (300-400 μV, 15 to 20 per minute) (Fig. 1, *I*, *b*). Resumption of ES during the period when epileptic activity was being generated in the focus resulted in complete suppression of spikes, which did not reappear on their own over the next 8-10 min of observation (Fig. 1, *I*, *c*).

Electrocoagulation of the SC led to resumption of epileptic discharges in 5 of the 7 rats (200-500 μV, 25-40 per minute) (Fig. 1, *I*, *d*). ES of the coagulated area altered neither the frequency nor amplitude of spikes in the focus (Fig. 1, *I*, *e*). In the other two rats, the amplitude of spikes decreased to 100-220 μV and their frequency to 15-20 per minute when the SC were stimulated during the period of stable epileptic activity; 3 to 5 stimulations were required for complete suppression of this activity. With ES, a focus of epileptic activity existed for 5 to 12 min, which was significantly less than in the control (without ES) ($p<0.01$). The percentage changes in the frequency and amplitude of spikes in the epileptic focus at the time of the first ES as compared to the values of these parameters 1 min before ES ($p<0.001$) and 1 min after the first ES ($p<0.05$) are shown in Fig. 1, *II*, *a* and *b*).

In the second series, we examined the effects of ES and of damage to the SC on a powerful focus of epileptic activity set up in the contralateral cortex by application of a 1% strychnine solution.

Preliminary observations (7 rats) showed that spike potentials of 380-450 μV appeared 4 to 7 min after strychnine application to the cortex and increased to 0.7-1.0 mV during the next 3-5 min (Fig. 2, *I*, *a*). They occurred at a frequency of 3-

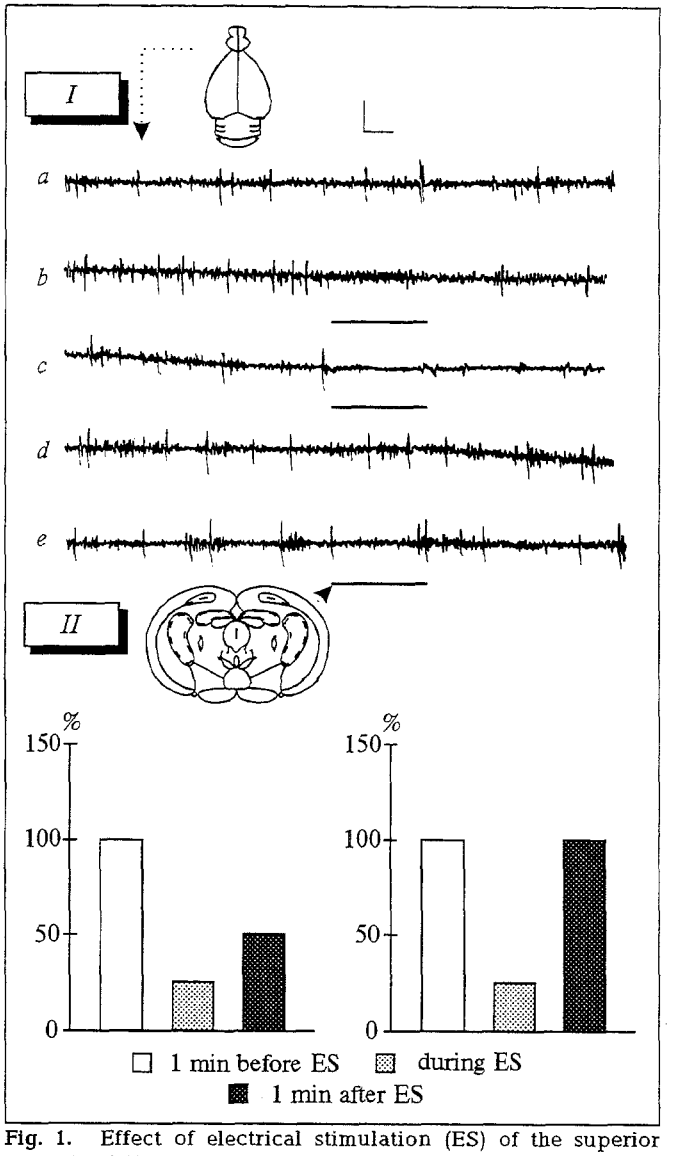

Fig. 1. Effect of electrical stimulation (ES) of the superior colliculi (SC) on a relatively weak strychnine-induced focus of epileptic activity (EpA) in the frontal region of the contralateral cerebral cortex. *I*. *a*) EpA 12 min after application of 0.1% strychnine solution to the frontal region; *b*) first ES session: 4 min after withdrawal of strychnine; *c*) second ES session: 3 min after start of ES; *d*) 5 min after electrocoagulation of the SC; *e*) 3 min after *d*: ES of the coagulated area. Stimulation is denoted by a solid line. ES parameters here and in Figs. 2 and 3: 10 Hz, 5 V, 0.25 msec. Time mark: 1 sec; calibration: 200 μV. *II*. Designations here and in Figs. 2 and 3: abscissa: light, dark, and hatched bars: 1 min before ES, during ES, and 1 min after ES, respectively. Ordinate: frequency (*a*) and amplitude (*b*) of spikes expressed in % of their values 1 min before ES taken as 100%.

8 per second. Activity in the focus remained stable for 12-19 min before decreasing in amplitude and frequency over the next 3-7 min to disappear completely. The focus of activity existed for 19-33 min.

When the SC were stimulated during the period of stable convulsive activity (7-12 min after strychnine application), the amplitude of spikes decreased to 200-400 μV and their frequency to

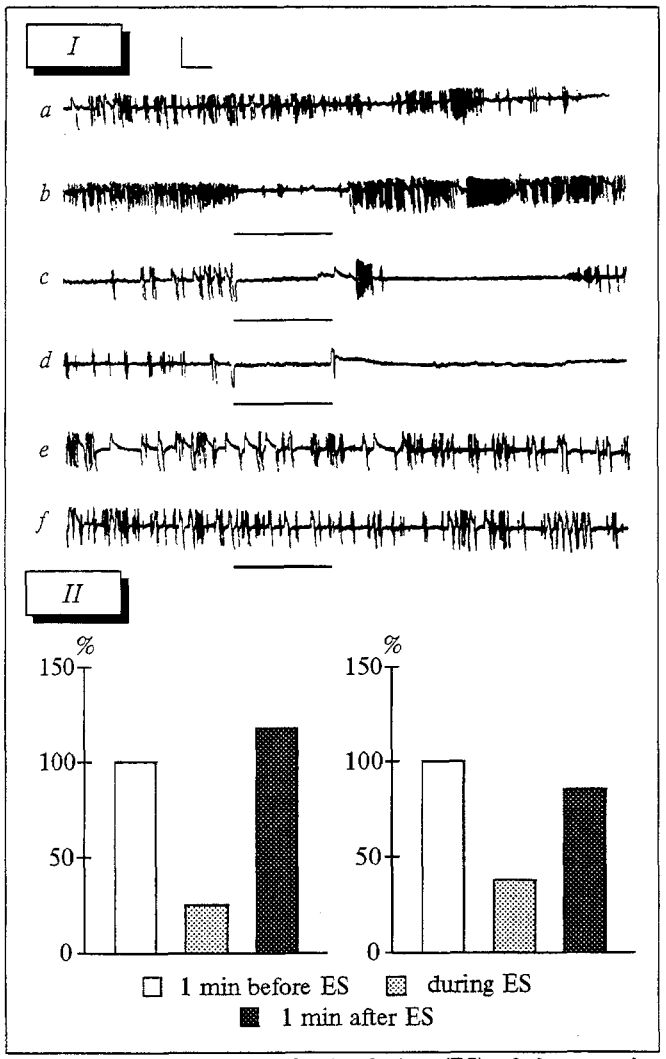

Fig. 2. Effect of electrical stimulation (ES) of the superior colliculi (SC) on a powerful strychnine–induced focus of epileptic activity in the frontal region of the contralateral cerebral cortex. *I*. *a*) 9 min after application of 1% strychnine solution; *b*) first ES session: 4 min after withdrawal of strychnine; *c*) third ES session: 4 min after *b*; *d*) fourth ES session: 2 min after *c*; *e*) 5 min after electrocoagulation of the SC; *f*) 3 min after *e*: ES of the coagulated area. Time mark: 1 sec; calibration: 500 μV.

0.7-2.0 per second (Fig. 2, *I*, *b*). Spikes of 0.6-0.9 mV in amplitude and 3-7 per second reappeared in the focus 3 to 6 sec after ES of the SC was discontinued (Fig. 2, *I*, *b*). This observation was made for 6 rats out of the 7 used in this test. Figure 2 (*II*) shows the percentage changes in the frequency (fragment *a*) and amplitude (fragment *b*) of spikes at the time of the first ES ($p<0.05$) and during the first minute after its discontinuation ($p<0.05$) in comparison with the values of these parameters during the first minute before ES. After 2 or 3 ES sessions, the amplitude of discharges in the focus was 0.7-0.9 mV and their frequency 0.8-3.0 per second (Fig. 2, *I*, *c*). When the SC were stimulated during that period, convulsive discharges were completely suppressed as long as ES was continued. After its discontinuation, spikes reappeared for a short time (2-5 sec) in 5 of the 7 rats tested, after which they were completely suppressed for 12 to 20 sec (Fig. 2, *I*, *c*). The convulsive discharges which then reappeared had amplitudes of 300-800 μV and occurred at a frequency of 1 to 5 per second (Fig. 2, *I*, *d*). ES of the SC at that time invariably led to a complete suppression of convulsive discharges which failed to reappear over the next 15 min of observation (Fig. 2, *I*, *d*). With ES, the focus of epileptic activity existed for 13-25 min, which is significantly less than without ES ($p<0.05$).

Electrocoagulation of the SC led, in 6 of the 7 rats tested, to a resumption of epileptic discharges (0.7-0.95 mV, 2-5 per second) (Fig. 2, *I*, *e*). ES of the SC after electrocoagulation failed to alter either the amplitude or the frequency of the spikes (Fig. 2, *I*, *f*).

In the third series, we examined how ES of the SC would affect an epileptic focus set up by application of a 0.1% strychnine solution in a cortical region ipsilateral to the side of ES. ES of the SC reduced the amplitude of spikes slightly to 200-230 μV and increased their frequency to 1-2 per second in 6 of the 7 rats tested (Fig. 3, *I*, *b*). After the discontinuation of the first ES, spikes of 350-470 μV, 20-30 per minute, were recorded during 1 min (Fig. 3, *I*, *b*) and spikes of 200-460 μV, 35-50 per minute, thereafter. The percentage changes in the frequency and amplitude of spikes in the epileptic focus at the time of the first ES ($p<0.001$ and $p<0.01$, respectively) and during 1 min after its discontinuation ($p<0.001$ and $p<0.05$, respectively) in comparison with the values of these parameters during 1 min before ES are shown in Fig. 3, *II*, *a* and *b*). During subsequent sessions of ES, the spikes had amplitudes of 200 to 270 μV and occurred at a frequency between 2 and 4 per second (Fig. 3, *I*, *c*). When ES was discontinued, spike potentials of 350-450 μV, 40-55 per minute, were recorded (Fig. 3, *I*, *c*) for 15-25 sec, followed by discharges of 250-500 μV, 25-40 per minute. The time during which the focus existed was 9-18 min and did not differ significantly from that in the control tests (without ES) ($p>0.05$).

These experiments have shown that high-frequency ES of the SC in rats leads to suppression of the epileptic activity induced in the contralateral frontal cortex by application of strychnine. Such ES decreased the amplitude and frequency of epileptic discharges and shortened the time during which the focus of epileptic activity existed. Simi-

lar effects have been produced by ES of other brain structures that are components of the antiepileptic system, such as the dentate and fastigial nuclei, cerebellar cortex, caudate nuclei, and caudal reticular nucleus of the pons [2,3,6]. In those experiments, however, ES suppressed epileptic activity in foci of low power while enhancing it in powerful foci. In the experiments described here, ES of the SC suppressed epileptic activity in both weak and powerful foci. Such differences may be ascribed to procedural differences, in particular to the use of Nembutal anesthesia, because drugs that activate the GABA-ergic mechanisms of the brain have been shown to eliminate those effects from ES of cerebellar structures which facilitate epileptic activity [8]. On the other hand, it is highly probable that activation of the SC contralateral to the focus of epileptic activity in the frontal cortex results in a greater inhibition of this activity than does ES of other antiepileptic structures. Possibly, the SC are a major component of the antiepileptic system. Thus, as shown earlier [4], introduction of penicillin (10-20 IU) into the SC brings about inhibition of generalized convulsive activity induced by systemic administration of picrotoxin to intact animals and those subjected to picrotoxin kindling as well as reducing the severity of convulsions produced by intraventricular injection of kainic acid. The observed antiepileptic effects of penicillin are due to its initiation of a generator of pathologically enhanced excitation in the SC [4].

The results of the present study also indicate that ES of the SC exerts its antiepileptic effects predominantly on foci of epileptic activity located in the contralateral cortex of the brain. A similar observation was made when cerebellar nuclei were electrostimulated [2]. Another contributing factor may be efferent connections of the SC with reticular structures of the brainstem, in particular the pons, which are predominantly contralateral [5,10].

In summary, high-frequency electrostimulation of the superior colliculi contralateral to an epileptic focus in the frontal cortex inhibits strychnine-induced focal epileptic activity in the cerebral cortex of rats, indicating that the superior colliculi may be an important component of the antiepileptic system of the brain. Indeed, they are likely to be a major antiepileptic structure.

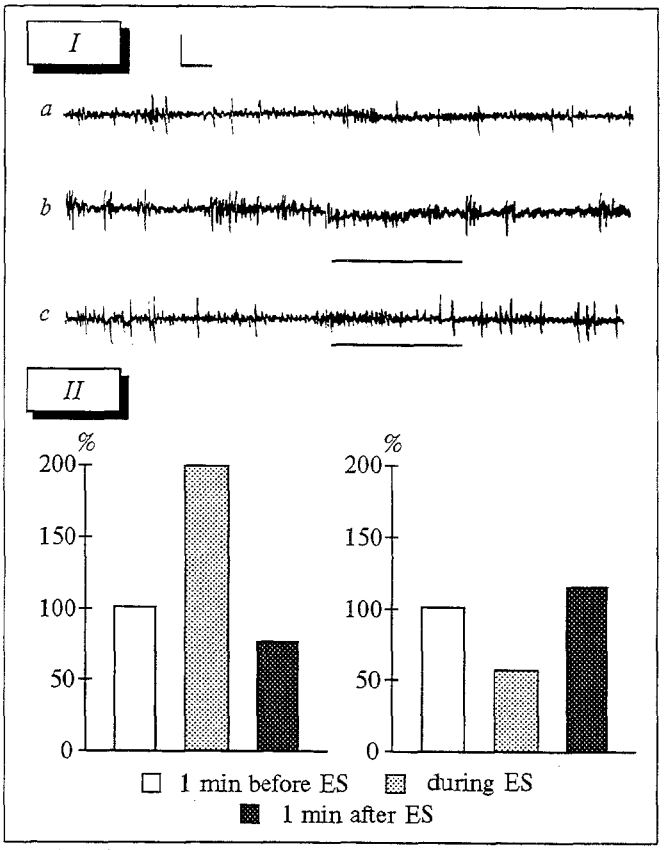

Fig. 3. Effect of electrical stimulation (ES) of the superior colliculi (SC) on a relatively weak strychnine-induced focus of epileptic activity in the frontal region of the ipsilateral cerebral cortex. *I. a*) 12 min after application of 0.1% strychnine solution; *b*) first ES session: 2 min after withdrawal of strychnine; *c*) third ES session: 4 min and 10 sec after *b*. Time mark: 1 sec; calibration: 200 μV.

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