Effects of antecedent footshock and current intensity on ECS-produced motor seizures in rats*

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The effects of antecedent footshock (FS) on ECS-produced motor seizures were examined. In two experiments, antecedent FS was shown to inhibit the tonic extension phase of the motor seizure without affecting a corresponding reduction in the duration of post-ECS coma. In addition, the incidence of tonic extension, but not the duration, of the ensuing coma was found to be positively related to ECS current levels between 20 and 40 mA. These results confirm previous reports of the effectiveness of FS in blocking ECS-produced tonic extension; however, these effects apparently do not reflect an overall reduction in the severity of the seizure.

A number of different motor seizure patterns can be produced by electroconvulsive shock (ECS) in rats, but at high current intensities a tonic-clonic seizure is typically produced (Golub & Morgan, 1944). With the application of current, there is an immediate flexion of the body followed by the onset of tonic extension. During the development of this tonic phase, the animal falls on its side and a "wave" of rigidity spreads caudally along the body until the back is arched and the forelimbs and finally the hindlimbs are fully extended. Seizures produced by ECS of lower intensity, however, usually completely lack this tonic phase or are marked by a partial tonus limited to the rostral portion of the body. As a result of this relationship between current intensity and tonus, the presence or absence of hindlimb extension has been widely used as a measure of the severity of an ECS-produced motor seizure. In fact, pharmacological blockage of ECS-produced hindlimb extension is generally accepted as strong evidence that a drug will be a clinically effective anticonvulsant (Woodbury, 1969). For example, the widely used anticonvulsant diphenylhydantoin (Dilantin) has been shown to abolish ECS-produced tonic extension while leaving the clonic activity intact or, in some cases, slightly prolonged (Toman, 1969).

Recently, Pinel (1971) demonstrated that a footshock (FS) administered to rats prior to ECS blocked the incidence of hindlimb extension, producing a motor seizure pattern characteristic of lower levels of ECS. This blockage was similar to that produced by diphenylhydantoin in that clonic activity was not reduced. This attenuation of ECS-produced hindlimb extension was found to be most frequent when FS-ECS intervals were short and FS durations were long. Gold and McGaugh (1972) confirmed the observation that antecedent FS blocks ECS-produced hindlimb extension,

but reported that this blockage occurred in the absence of any obvious attenuation in the underlying electrographic afterdischarges. In fact, the secondary afterdischarge was significantly longer in FS-treated animals.

The fact that sensory stimulation can have an anticonvulsant effect has been widely reported in both the experimental (e.g., Guerrero-Figueroa, Barros, & De Balbain Verster, 1963) and clinical (e.g., Jung, 1963) literature; however, there have been few systematic studies of this effect. Until the potential of sensory stimulation in abolishing seizure activity has been delineated, the possibility of applying such techniques for therapeutic purposes should not be ruled out. The purpose of the present experiments was to explore in more detail the FS-produced blockage of ECS-produced motor seizures.

EXPERIMENT I

Following completion of ECS-produced tonus and the subsequent clonic phase, the organism typically lapses into coma. Although coma duration has been found to be correlated with the severity of central nervous system trauma in a number of clinical situations, this aspect of ECS-produced seizures has not been systematically studied. The purpose of Experiment I was to examine the effects of antecedent FS on both the tonic extension and comatose phases of ECS-produced seizures in rats.

Method

Subjects

The Ss were 12 male 200-250-g hooded rats purchased from the Canadian Breeding Laboratories. They were individually housed with continuous access to food and water for the duration of the experiment.

Surgery

Electrodes were constructed by soldering a 2-cm metal alloy rod (1-mm diam) to a stainless steel skull screw. Following

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Fig. 1. Effects of footshock (FS) on the hindlimb extension and comatose phases of ECS-produced motor seizures.

sodium pentobarbital anesthesia (50 mg/kg, IP), the electrodes were screwed into the skull until they made contact with the underlying dura at bilaterally symmetrical points 2 mm posterior to bregma and 4 mm lateral to the midline. Dental acrylic was used to hold the screws in place and to insulate them from the surrounding tissue. During ECS administration, leads were attached to the rods, which protruded approximately 1 cm above the surface of the dental acrylic.

Apparatus

All tests were conducted in a Plexiglas chamber (25 x 25 x 40 cm) with a grid floor of 1/8-in.-diam copper alloy bars placed 1/2 in. apart and wired to deliver FS. Both the 0.5-sec, 20-mA, 60-Hz ECS and the 5-sec, 2-mA, 60-Hz FS were administered from constant current sources and were automatically timed. During administration of the FS, the ECS leads were automatically disconnected from the apparatus to minimize the possibility of short circuits through the neuraxis.

Procedure

Three days following surgery, all Ss were placed in the apparatus and the ECS leads were attached. This procedure was repeated on the next 2 days. Beginning on the 4th day of the experiment, ECS was administered once a day for 3 days. FS was administered 1 sec prior to the third and final ECS administration. During recovery from coma on each of the 3 ECS days, a 90-dB 15,000-Hz tone was sounded for 5 sec at 5-min intervals. The coma was assumed to be complete after the S had righted himself and had made a walking movement involving all four legs.

One S suffered from ECS-produced paraplegia, and his data were not included in the analysis.

Results and Discussion

Two types of motor seizure pattern were observed: (a) a full tonic-clonic pattern involving initial tonic flexion followed by tonic extension, clonus, and postictal coma, and (b) a pattern in which hindlimb

extension was completely or partially attenuated. The effects of antecedent FS on the incidence of these two types of seizure is clearly evident in Fig. 1. When ECS was administered alone, the incidence of hindlimb extension was about 80%, but when FS preceded ECS, hindlimb extension occurred in only 18% of the cases. The difference between the incidence of hindlimb extension on Days 2 and 3 was statistically evaluated, using the McNemar test for significance of changes with the correction for continuity (Siegel, 1956) and was found to be significant ($\chi^2 = 4.5$, $df = 1$, $p < .05$). Figure 1 also shows that this FS-produced abolition of hindlimb extension occurred in the absence of any obvious effects on the duration of the coma as operationally defined in this particular experiment. A comparison of the coma duration on Days 2 and 3 using a *t* test for correlated samples (Ferguson, 1959) confirmed that these differences were not statistically significant ($t = 1.4$, $df = 10$, $p > .05$).

These results confirm the previous reports of Pinel (1971) and Gold and McGaugh (1972), that FS markedly attenuates the tonic component of ECS-produced motor seizures. There was, however, no evidence to suggest that FS produces a corresponding reduction in the duration of coma.

EXPERIMENT II

The effects of antecedent FS on ECS-produced motor seizures are not independent of the ECS current parameters. Pinel (1971) administered FS prior to ECS of two different current intensities, both of which regularly produced complete tonic-clonic seizures. Blockage of hindlimb extension by FS was found more frequently at the lower current level. Thus, the possibility exists that the lack of FS-produced effects on coma duration may also be a function of the particular ECS intensity employed. The purpose of Experiment II was to test the generality of the effects observed in the first experiment by administering FS prior to different levels of ECS. In the process, the relationship between coma duration and ECS intensity was examined.

To provide an additional basis for assessing the generality of the results of Experiment I, a basically different experimental design was employed. Rather than repeatedly administering ECS to the same Ss, each animal in Experiment II was subjected to only a single ECS treatment.

Method

Subjects

Serving as Ss in Experiment II were 60 male hooded rats purchased from the Canadian Breeding Laboratories. These Ss were larger than the Ss used in Experiment I, weighing between 250 and 450 g.

Apparatus

The apparatus was the same as that employed in Experiment I.

Procedure

Surgical procedures were identical to those used in Experiment I. Following recovery from surgery, each of the 60 Ss received a single .5-sec 60-Hz ECS of 10, 20, or 40 mA. Half of the 20 Ss receiving an ECS at each current level received an antecedent 5-sec, 2-mA, 60-Hz FS 1 sec prior to the ECS.

Results

The effects of ECS current intensity and FS on the incidence of hindlimb extension are summarized in Fig. 2. The relationship between ECS current intensity and hindlimb extension was similar to that previously reported by Golub and Morgan (1944). As current intensity increased, hindlimb extension became more prominent in the no-FS animals. According to the Fisher exact probability test (Siegel, 1956), the incidence of hindlimb extension in both the 10-mA and 20-mA no-FS groups was significantly less than in the 40-mA no-FS group ($p < .05$). In addition, FS was clearly shown to have an inhibitory effect on tonic extension. This effect, however, was significant only ($p < .05$; Fisher exact probability test) at the 40-mA level, since the low incidence of tonic hindlimb extension in the control animals at the two lower current levels precluded the demonstration of a significant inhibitory effect.

The effects of current intensity and FS on the incidence of tonic extension were not reflected in the coma duration data. A 2 by 3 analysis of variance (Ferguson, 1959) performed on these data revealed that neither FS ($F < 1$, $df = 1/54$, $p > .05$), current intensity ($F < 1$, $df = 2/54$, $p > .05$), nor the interaction between them ($F = 1.4$, $df = 2/54$, $p > .05$) had any significant effect on coma duration. Thus, although both FS and current intensity had significant effects on tonic extension, coma duration in these same animals was unaffected.

DISCUSSION

In both Experiments I and II, antecedent FS disrupted the tonic extension phase of ECS-produced motor seizures, thus confirming the previous reports of Pinel (1971) and Gold and McGaugh (1972). These inhibitory effects, however, were produced in the absence of any significant changes in the duration of the ensuing coma. Thus, it seems that FS can disrupt ECS-produced motor seizures without affecting an overall decrease in the severity of the trauma.

It has been widely reported that a variety of sensory stimuli, including FS, can be used to block seizures produced in experimental animals (Pinel, Phillips, & MacNeill, 1973; Pinel & Chorover, 1971) as well as spontaneous seizures occurring in human epileptics

Fig. 2. Effects of current intensity and footshock (FS) on the incidence of ECS-produced tonic hindlimb extension.

(Jung, 1962). In many of these cases, this blockage seems to be produced by the direct action of the sensory stimulation on the cerebral electrographic epileptiform activity. For example, both Pinel and Chorover (1971) and Guerrero-Figueroa, Barros, and De Balbian Verster (1963) reported an immediate cessation of peti-mal-like electrographic activity with the presentation of any of a variety of visual, acoustic, olfactory, and tactile stimuli, including FS. In contrast, the FS-produced blockage of ECS-produced seizures appears to take place at lower levels of the nervous system. FS produces no reduction in either electrographic or behavioral measures of ECS-produced cerebral trauma, even though there is a striking attenuation of tonic extension. Apparently, FS and other arousing stimuli can inhibit seizures by blocking the triggering of cerebral afterdischarges or by acting directly on spinal and peripheral motor mechanisms. It is not unexpected that disruption of ECS-produced motor seizures can occur at the spinal level in view of the work of Esplin (1959). He found that the typical tonic-clonic pattern could be produced in cats, rabbits, rats, hamsters, and mice after complete section of the neuraxis below the medulla by applying gross electrical stimulation to the severed end of the cord, even when cerebral structures were destroyed. Furthermore, motor seizure activity, once initiated, outlasted the period of stimulation. Thus, although ECS-produced seizures are undeniably triggered by cerebral afterdischarges, the actual patterning of the seizure is apparently controlled by spinal mechanisms.

The fact that the inhibitory effects of arousing stimuli on ECS-produced motor seizures can occur at two levels

of the nervous system is reflected by the effects of certain anticonvulsants on ECS-produced motor seizures. For example, both Dilantin (Stille & Sayers, 1967) and sodium pentobarbital (Jamieson, 1972) have been shown to block ECS-produced motor seizures, but only sodium pentobarbital eliminates the electrographic afterdischarges.

Even though the blockage of ECS-produced extension does not necessarily reflect a change in the underlying electrographic activity, the disruption of tonic extension has been one of the most valuable signs that a drug will be a clinically effective anticonvulsant (Swinyard, 1969). The drug Dilantin, for example, has been one of the most widely used and effective anticonvulsants. Its effects on ECS-produced seizures, however, are almost identical to those produced by FS. Dilantin blocks ECS-produced tonic extension while exacerbating the clonic component (Millichamp, 1969) without markedly affecting the cortical afterdischarges (Stille & Sayers, 1967). This similarity of the effects of FS and Dilantin on this commonly used assay for anticonvulsant drugs serves to underline the possibility of using sensory stimulation in the control of epilepsy.

The present results also have implications for studies of ECS-produced amnesia. Since most animals tested at high current levels have very stereotyped tonic-clonic seizures, the impression is that the ECS is having comparable effects on all animals. Often those animals not displaying tonic hindlimb extension are deleted from these experiments because they have not had maximal seizures comparable to those of the other Ss. The present results, however, show that two animals displaying the same stereotypical motor seizure pattern can have been affected by the ECS quite differently. In our experiments, animals receiving the same level of ECS and displaying the same maximal motor seizure pattern varied greatly in their duration of coma. Following maximal seizures, Ss remained comatose for as little as 2 min or as long as 3 h. The factors underlying this variability as well as its effect on the level of ECS-produced amnesia should be explored.

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