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Effects of prolonged weak anodal direct current on electrocorticogram in awake rabbit.

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Abstract

The effects of prolonged weak anodal direct current (DC) on the electrocorticogram (ECoG) were investigated in awake rabbits. When the current (20-40 microA) was applied to the motor region of the cerebral cortex, seizure activity in the ECoG appeared from the frontal cortex. Repeated application of the DC decreased the threshold current for producing the seizure activity. Diazepam significantly elevated the threshold of the seizure activity. In contrast to the marked changes in the ECoG, no behavioral changes were observed during or after the application of weak anodal DC. The changes in the ECoG are discussed in relation to the intensity and duration of the DC.

KEYWORDS: rabbit cerebral cortex, anodal direct current, electrocorticogram, seizure activity, diazepam

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—Brief Note—

Effects of Prolonged Weak Anodal Direct Current on Electrocorticogram in Awake Rabbit

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The effects of prolonged weak anodal direct current (DC) on the electrocorticogram (ECoG) were investigated in awake rabbits. When the current (20-40 μA) was applied to the motor region of the cerebral cortex, seizure activity in the ECoG appeared from the frontal cortex. Repeated application of the DC decreased the threshold current for producing the seizure activity. Diazepam significantly elevated the threshold of the seizure activity. In contrast to the marked changes in the ECoG, no behavioral changes were observed during or after the application of weak anodal DC. The changes in the ECoG are discussed in relation to the intensity and duration of the DC.

Key words : rabbit cerebral cortex, anodal direct current, electrocorticogram, seizure activity, diazepam

Although several authors have reported that application of anodal direct current (DC) through the cortex produced seizure activity in the electrocorticogram (ECoG) (1-3), the applied current was so strong that it caused a lesion in the tissue surrounding the tip of the electrode. Recently, Sunami (4) observed that transcortically applied weak anodal DC, which did not cause any noticeable damage to the tissue, produced cortical seizure activity in anesthetized rabbits. In the present study, we investigated the effect of repeated application of weak anodal DC through the motor region of the cortex on the ECoG pattern in awake rabbits. In addition, we examined whether behavioral changes, such as tremor and convulsion, would occur under these conditions.

Seven male albino rabbits weighing 2-2.5 kg were used for the study. For application of anodal DC and recording of the ECoG, fourteen silver wire electrodes (1 mm in diameter) were bilaterally implanted in the cranial bone under sodium pentobarbital anesthesia as shown in Fig. 1. These electrodes were located rostrocaudally on a parasagittal line at a distance of 3 mm from the midline. The distance between electrodes was 2.5 mm. The animals were allowed at least 10 days after surgery to recover before the experiments were begun. DC application methods were essentially the same as described previously (5). DC was continuously applied between one of the silver wire electrodes implanted in the cranial bone over the motor cortex (anode) and a

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silver plate (3×6 cm) which was attached to the ear lobe (cathode). The current was gradually raised in steps of 10 μA from 10 μA to the intensity which induced seizure activity in the ECoG. The maximum intensity of current was less than 300 μA. The current at each step was maintained for 2 min. When generalized seizure activity appeared, the current was turned off. This procedure was repeated three times at intervals of 20 min in each of four rabbits. The current intensity which produced the initial seizure activity was taken as the threshold current. One week after the first series of experiments, diazepam (3 mg/kg) was administered intravenously 30 min before the DC application. In the other three rabbits, the current which was sufficient to induce generalized cortical seizure activity was applied, and we examined whether any behavioral changes occurred in the course of generalized seizure development. In these animals, the maximum intensity of the current was up to 500 μA and the DC application was performed once a day for 6 or 7 weeks.

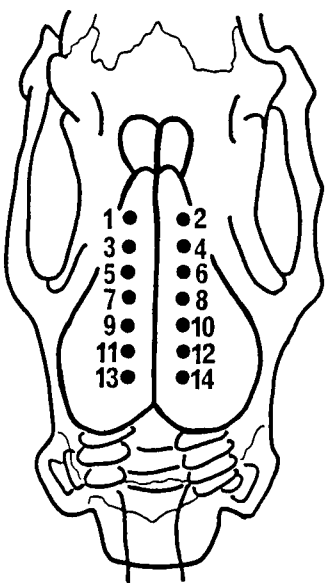

Fig. 1 Schematic diagram of the location of silver wire electrodes for ECoG recording (Nos. 1-8, 11-14) and DC application (Nos. 9, 10).

Fig. 2 shows seizure activity in an ECoG induced by prolonged anodal DC. The seizure activity was observed only in the frontal cortex when the current intensity was 20 μA. When stronger current was applied, more frequent spikes, sharp waves and augmentation of slow waves were observed. In this case, seizure activity was observed in almost all parts of the cortex. When the current was turned off, seizure activity promptly disappeared and no depression was left in most cases. In some cases, seizure activity in the ECoG continued in a few regions of the cortex even after the cessation of the current (Fig. 2, D). It is possible that the seizure activity is derived from artifacts. However, we excluded this possibility, since in rabbits treated with diazepam, a popular anticonvulsant, no seizure activities in the ECoG were observed when the intensity of the DC was below 150 μA (Fig. 3). When the DC was applied three times at intervals of 20 min, the threshold current for the initial seizure activity tended to decrease with each trial (Fig. 3). Furthermore, the initial seizure activity always appeared from the frontal cortex in all animals. There were no behavioral changes when the generalized seizure activities in the ECoG appeared following repeated application of anodal DC for 6 or 7 weeks (data not shown).

It has been reported that anodal DC induces seizure activity in the ECoG when applied transcortically (1-3). Tsuru *et al.* (3) observed in cats that anodal DC was more effective in producing seizure activity than cathodal DC, and that the seizure activity was induced by anodal DC at the intensity of 1.6 mA. In our present experiment, the initial seizure activity, which appeared mostly from the frontal cortex, was evoked at the

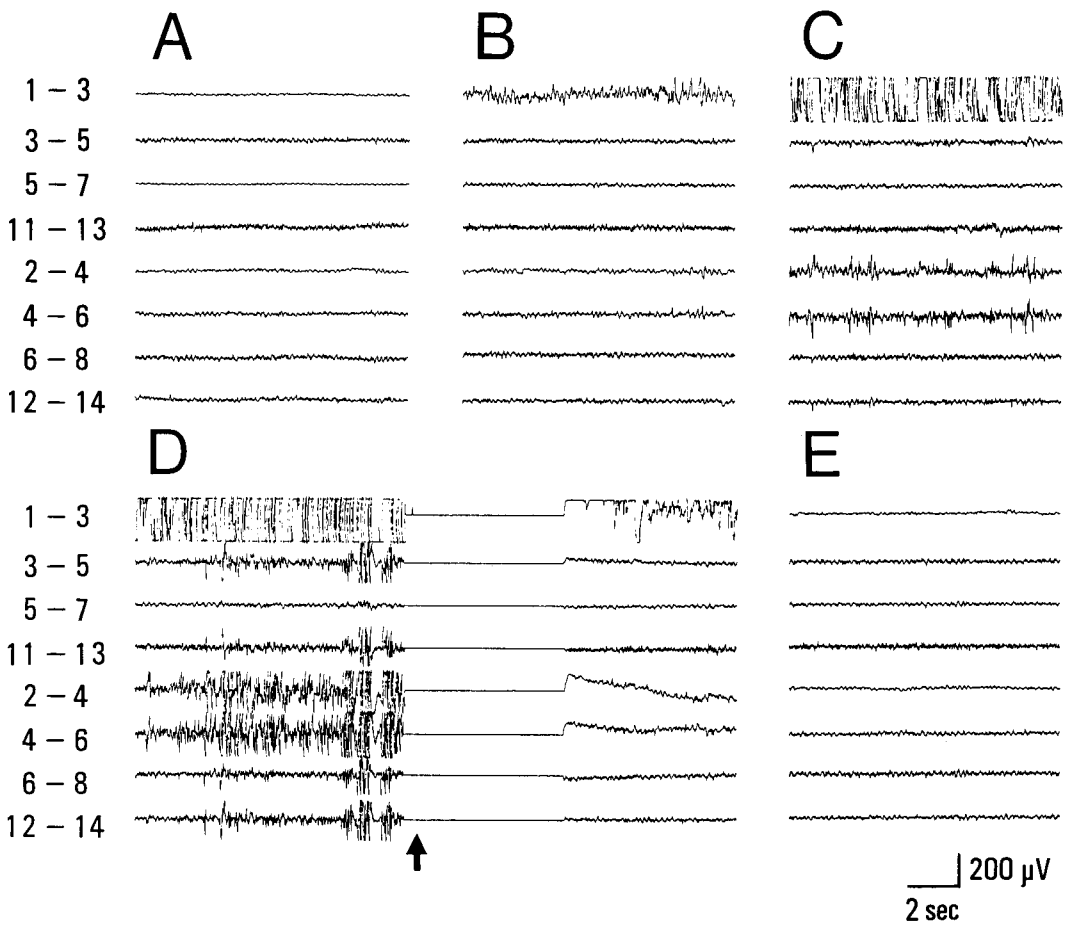

Fig. 2 Development of cortical seizure activity induced by anodal DC application. The current was applied to electrode No.9. A represents the ECoG pattern before DC application. B, C and D represent the pattern during DC application at the intensity of 20, 40 and 60 μA, respectively. E represents the pattern 5 min after DC was terminated. The arrow indicates the turning off point of DC. The numbers left of the ECoG indicate the recording electrodes.

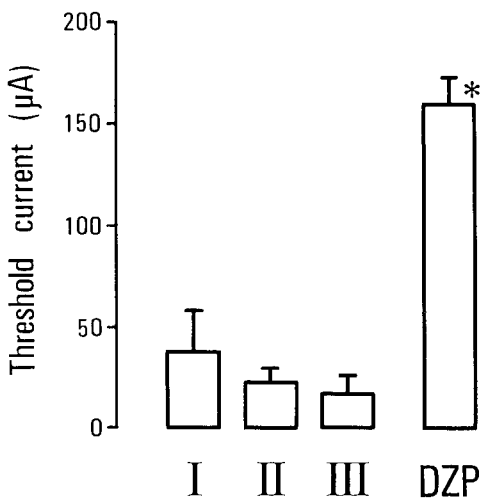

Fig. 3 Effect of repeated DC application at intervals of 20 min and the effect of diazepam on the threshold for initial seizure appearance. I, II, III and DZP indicate the first, second, third and diazepam administration trials, respectively. Each value represents the mean ± SEM of 4 different experiments. *: Significantly different from the first trials determined by Mann-Whitney U-test ($p < 0.05$).

intensity of 20-40 μA. This threshold was much lower than those previously reported (1-3). It was not possible to simply compare the threshold current observed in the present experiment with those reported by others, because of the differences in the experimental methods, animal species, duration of stimulation and so on. It is likely that the threshold for inducing the seizure activity in the ECoG is dependent on both the duration and the intensity of the DC. The present experiments demonstrated that far weaker DC is enough to induce seizure activity in the ECoG when applied for a long enough time. It was curious that no abnormal motor activity, such as tremor or convulsion, were observed even when severe seizure activities in the ECoG were going on over a wide region of the cortex. Leão (6) reported that similar seizure activity appeared along with cortical spreading depression, but not with behavioral convulsive activity. Cortical seizure activity induced by anodal DC might be independent of behavioral convulsions, or parts of the brain region other than the cortex may play a role in behavioral convulsions. Alternatively, more intense seizure activity in the ECoG might be necessary to elicit behavioral changes. When the current was applied repeatedly, the threshold current for producing seizure activity decreased, thereby suggesting that anodal DC might induce some plastic change in the rabbit cerebral cortex.

There have been few reports concerning the effects of anticonvulsants on cortical seizure activities evoked by anodal DC. We examined the effect of diazepam, a very popular anticonvulsant, on the seizure activity in the ECoG. Diazepam produced a significant elevation of the threshold current for the initial seizure activity. This result suggests that the seizure activity induced by weak anodal DC is a useful model of epilepsy. Further studies are underway to characterize the ECoG seizure activity elicited by prolonged weak anodal DC.

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