FURTHER OBSERVATIONS ON THE SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX

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THE *spreading depression of activity*, a response elicited by local stimulation of the cerebral cortex, has been described previously (4). Briefly, this response consists of a marked, enduring reduction of the "spontaneous" electrical activity, a reduction which appears first at the region stimulated and spreads out from there in all directions, involving successively more and more distant parts of the cerebral cortex. The rate of spread is slow: in rabbits, under dial, a response started in the frontal region takes 4 or 5 minutes to reach the occipital pole. Recovery of the initial pattern of "spontaneous" electrical activity requires 5 to 10 minutes at each region. Specific electrical activity, different from the "spontaneous," often develops during the period of depression in some cortical regions. This activity, when intense, closely resembles the "seizure pattern" of experimental epilepsy.

The following study considers another aspect of this response: a slow voltage variation, having a duration of several minutes.

METHODS

The experiments were performed on rabbits, under dial anesthesia (0.6 to 0.7 cc. per kg.), with one cerebral hemisphere widely exposed. Stimulation of the cortex was carried out as a rule with an induction coil, as previously (4). The lead-off electrodes were of the silver-silver chloride-Ringer agar type, with a cotton wick trimmed to a point. One of these was applied to the surface of the pia-mater, and the other, which served as a reference electrode, was ordinarily applied to the bone near the external occipital protuberance.

The bioelectrical phenomena were measured with a string galvanometer, either connected directly or used with an electron tube balanced pre-amplifier, of high input impedance. Sudden anemia of the cortex was produced, as in a previous study (6), by clamping temporarily the common carotid arteries of an animal with the basilar artery occluded at the level of the pons (with a silver clip), and the external carotid arteries tied just above their origin.

RESULTS

When the electrodes were connected as above, a steady voltage difference was ordinarily observed. The rapid variations which constitute the "spontaneous" electrical activity of the cortex were superimposed on this difference. In this paper, this difference will be referred to as the "normal" voltage of any given cortical region.

A. Slow voltage variation accompanying the spreading depression of activity. If a spreading depression of activity was produced anywhere in the cortex, by any of the known modes of elicitation (4, 6), a voltage variation having a duration of several minutes was observed which commenced when the response reached the region of the cortical electrode (Fig. 1). The affected region at first showed a negativity which increased to a maximum value of 7 to 15 mV within about 0.5 to 1 minute. It then decreased, often somewhat more rapidly. The voltage passed through its normal value about 1.5

minutes (1 to 2 min.) after the beginning of the variation, the cortex then becoming positive with respect to the reference electrode. Maximum positivity was as a rule reached less than 0.5 min. after the beginning of the positive phase. The positive voltage then decreased slowly, and disappeared after 3 to 5 min. This positive phase had a smaller amplitude than the negative; in many instances its amplitude was less than half that of the preceding negative phase. The complete variation lasted therefore about 4 to 6 min. Occasionally, a small positive voltage shift, of less than 0.5 mV, was observed before the onset of the initial negative phase.

This slow voltage variation exhibited the same general features in all the

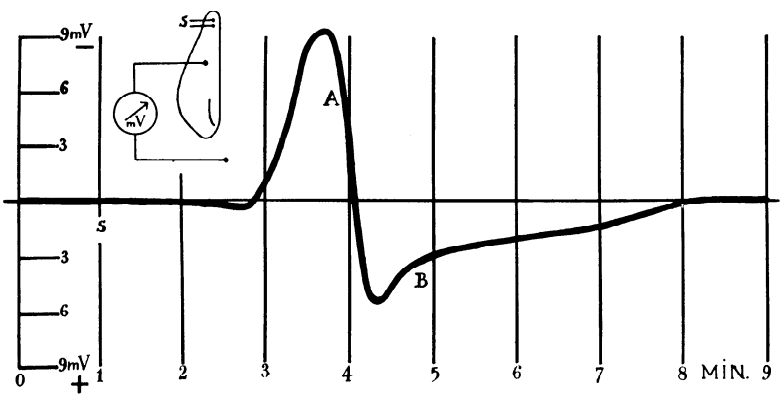

FIG. 1. A representative experiment on the slow voltage variation accompanying the spreading depression of activity. The curve was drawn from voltage readings taken with 5-second intervals. In this and the other two figures, an upward deflection denotes negativity of the cortex, with respect to the extracortical reference electrode. Electrodes arranged as shown in the inset (s: stimulating electrodes). Stimulation, 5 seconds of "tetanizing" current from an induction coil, delivered at the time marked S. In this representative curve is indicated the time of occurrence (from A to B) of the specific electrical activity which often develops during the depression of the "spontaneous."

regions of the convexity of the hemisphere which were involved in the response. No attempt has been made, however, to investigate in detail the existence of minor regional differences. From the stimulated region, where it appeared first, it spread out in all directions, appearing at any given region coincidently with the changes, already described, in the electrical activity and excitability of the cortex (4) and in the pial circulation (5). As the negativity increased, the "spontaneous" electrical activity of the region began to decrease, and the pial arteries to dilate. The specific electrical activity which often develops during the depression of the "spontaneous," occurred when the voltage of the region, having passed through its maximum negative value, was changing from negative to positive, and continued during the early part of the positive phase (from A to B, Fig. 1). Later in this last phase the "spontaneous" electrical activity began to reappear.

B. Effects of cortical anemia, for periods up to 1 minute in duration. A sudden cortical anemia, resulting from an arterial occlusion (cf. Methods) maintained for 1 minute, causes complete cessation of the "spontaneous"

electrical activity (6). Recovery occurs in the course of several minutes following re-establishment of circulation. Such 1-min. periods of acute anemia did not of themselves induce any appreciable variation of the normal voltage of a cortical region. This was true (i) if the cortex had not been stimulated, (ii) if it had been previously stimulated at a distant region, so as to initiate there a spreading depression of activity, which did not reach the region in consideration before the period of anemia was completed, or (iii) if, in the course of a spreading depression of activity in the hemisphere, the arterial occlusion was produced after the response had passed through the region in question. These periods of sudden anemia had, however, a very marked effect on the voltage of any cortical region if produced while the spreading depression was occurring in this region. Under these circumstances, interruption of the circulation promptly and profoundly increased the negative phase of

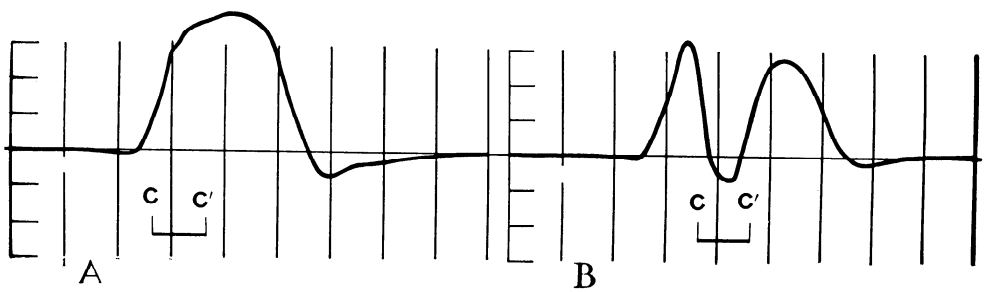

FIG. 2. Effects of short periods of sudden acute cortical anemia on the slow voltage variation accompanying the spreading depression of activity. Arrangement of electrodes and stimulation as in Fig. 1. Stimulation delivered at the time marked S. From C to C', the 1-minute period of arterial occlusion.

the slow voltage variation accompanying the spreading depression. This alteration outlasted (up to 2 min.) the period of arterial occlusion.

If the period of anemia coincided with the early part of the negative phase of the variation described above, then this phase was longer and almost always reached a somewhat higher voltage than usual. The ensuing positive phase was, on the other hand, decreased (Fig. 2A). If the period of arterial occlusion coincided with the decline of the negative phase or the initiation of the positive, a second negative peak promptly appeared in the voltage curve. The following positive phase was correspondingly decreased or even in some instances abolished (Fig. 2B). If the arteries were occluded later in the positive phase, the effect was less intense; a small break towards negativity was produced, after which the positivity continued its slow course of subsidence. This effect was progressively less intense, so that towards the end of the positive phase the 1-minute interruptions of the circulation did not give rise to any appreciable voltage variation.

The specific electrical activity which often occurred during the depression was promptly abolished during these short periods of sudden cortical anemia, which, as shown elsewhere (6), do not interfere with the spreading depression.

C. Effects of prolonged cortical anemia. In a cortex, in no part of which

a spreading depression was in progress, interruption of the circulation for longer periods induced of itself a slow voltage variation. This variation appeared only 2.5 to 5 minutes after the beginning of the arterial occlusion, at which time the cortex became negative with respect to the extracortical reference electrode. The negativity developed identically to that produced by a spreading depression of activity (Fig. 3A), and usually reached a slightly higher voltage. The cortex then remained negative for as long as the arteries were occluded. Observations were made for periods of anemia up to 12 min. in duration; in certain cases, there was a slight decline from the maximum negativity reached in the first few minutes.

Experiments carried out with five electrodes placed on different cortical regions, and successively connected, every 10 seconds, to the galvanometer,

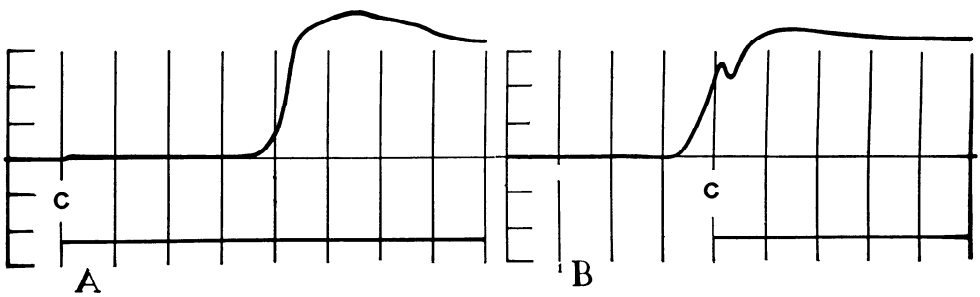

FIG. 3. Effects of prolonged interruption of the cortical circulation. A: Arterial occlusion started at C, and maintained until after the 9th minute. The cortex had not been stimulated. Lead-off electrodes arranged as in Fig. 1. B: The arteries were occluded at C, while the region of the cortical electrode was involved in a spreading depression of activity and exhibiting the slow voltage variation. Arrangement of electrodes and stimulation as in Fig. 1. Stimulation delivered at the time marked S. The occlusion was maintained until after the 9th minute. Note that the decline of the negative phase of the voltage variation accompanying the response was prevented, shortly after its beginning, by the sudden cortical anemia.

showed that the negativity induced by prolonged anemia did not develop simultaneously in all regions. As a rule, one part of the hemisphere became negative first, and then the others in succession, usually with a difference of 1 or 2 minutes, or more, between the onset of the change in the first and the last. When the cortical circulation was re-established, the negativity subsided slowly and disappeared in a few minutes. As a rule, this regression was slower the longer the region had remained negative, and it was in most cases preceded by a temporary increase in negativity.

If the prolonged anemia was started while a cortical region was involved in a spreading depression of activity and exhibiting the slow voltage variation, then the negativity promptly induced in the region persisted for as long as the circulation was interrupted (up to at least 12 minutes) (Fig. 3B). After the carotids were released, the negativity subsided as described above.

COMMENT

The experiments described above suggest interesting paths of inquiry

into the nature of the processes which take place during the spreading depression of cortical activity. The areas involved in a spreading depression exhibit a distinctive susceptibility to sudden interruption of the circulation. This susceptibility is revealed by the prompt occurrence of some change, which in a region not actually involved in that response, appears only after a certain time. The electrical sign of this change is the negative voltage variation. The susceptibility prevails at a time when the voltage of the cortical region, otherwise stable for hours on end, is varying in consequence of a stimulation which initiated the spreading depression of activity. These facts seem to indicate that in this response some change of the same nature as one resulting from prolonged interruption of the circulation occurs in the cerebral cortex. In the response, there is quick recovery, provided the cortical blood supply is adequate, as the negative voltage variation travels over the hemisphere. Occlusion of the arteries promptly prevents this recovery. For example, in the experiment illustrated in Figure 3A, the negativity was induced by the cortical anemia itself, and appeared only more than 3 minutes after the arterial occlusion. In B, a similar negativity developed during the response to stimulation, and interruption of the circulation prevented its regression. The study of the causes of the negativity resulting from acute anemia may therefore bring valuable information on the nature of the depression of activity in the cerebral cortex and its propagation.

This cortical voltage variation—induced by interruption of the circulation—resembles closely, in many respects, the variations described by van Harreveld (9), which develop in the spinal cord during asphyxiation. This author believes that the voltages recorded in the spinal cord deprived of oxygen are the expression of the depolarization of the normally polarized membrane of the neurones. More data than those here presented are needed for an adequate discussion of the possible causes of the cortical negativity, and for a proper examination of the application of this hypothesis to the cortical voltage variations which occur under the two different sets of conditions.

In this connection, the study of steady voltage differences in the cortex is important. These have been considered by Libet and Gerard, who in a series of studies (2, 3, 7, 8) on the isolated frog brain have described many phenomena which may have a bearing on the investigation of the cortical response considered in this paper. It is hoped that future studies may correlate these two sets of data more closely.

Dusser de Barenne and McCulloch (1) have described slow voltage variations in the monkey cerebral cortex, which seem to resemble those shown here to accompany the spreading depression of cortical activity in the rabbit.

Summary

A slow voltage variation having a duration of 4 to 6 min. accompanies the spreading depression of activity in the rabbit's cerebral cortex. Each cortical region first becomes negative with respect to an extracortical reference electrode, for 1 to 2 min. This negativity reaches, within 0.5 to 1 min.

a maximum of 8 to 15 mV and then decreases somewhat more rapidly. The region then becomes positive for 3 to 5 min., this phase having usually a smaller amplitude than the negative (Fig. 1).

A sudden cortical anemia, resulting from a 1-minute arterial occlusion, abolishes the "spontaneous" electrical activity of the cortex without itself inducing a slow voltage variation, but it promptly and profoundly alters the slow voltage variation accompanying the spreading depression of activity. This alteration consists essentially of a prolongation and an increase of the negativity (Fig. 2). In a cortex, in no part of which a spreading depression of activity is in progress at the time, interruption of the circulation for longer periods induces a slow voltage variation only 2.5 to 5 min. after the arterial occlusion, at which time the cortex becomes negative (Fig. 3A). The cortex then remains negative for as long as the circulation is interrupted (up to at least 12 min.).

If the prolonged anemia is started while a region is involved in a spreading depression of activity and exhibiting the slow voltage variation, then the negativity, promptly induced in the region, persists for as long as the arteries are occluded (up to 12 min.) (Fig. 3B).

The results seem to indicate that in the spreading depression of activity, a change of the same nature as one resulting from prolonged interruption of the circulation, occurs in the cerebral cortex. The electrical sign of this change is the negative voltage variation.

I wish to express my gratitude to Prof. Carlos Chagas Filho for his valuable and friendly interest in this study. The work was aided, in part, by a grant made to him by The Rockefeller Foundation.

Note: Shortly before this paper was sent to press, I received a letter from Dr. B. Libet, of the University of Chicago, in which he tells that Dr. R. W. Gerard and himself, in an investigation on the steady voltage gradients in the brain and their changes in relation to excitability changes induced by various means in the neurones, have also observed the slow voltage variation accompanying the spreading depression of activity in the rabbit's cerebral cortex. I was delighted to know that their description of the variation is in agreement with that presented in this paper (Results—Section A).

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