PIAL CIRCULATION AND SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX

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THE SPREADING depression of activity, a response elicited by electrical or mechanical stimulation of the cerebral cortex, has been described by Leão (8).

Briefly, this response consists of a marked, enduring reduction of the electrical activity, a reduction which appears first at the region that has been 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 narcosis, a response started near the frontal pole may take more than 5 minutes to reach the occipital pole. Recovery of the initial pattern of spontaneous electrical activity requires 5 to 10 minutes, or even more, at each region.

The present paper describes changes that have been observed to occur in the pial circulation simultaneously with the depression of the cortical electrical activity and its spread.

METHODS

Rabbits, under dial narcosis (0.55 to 0.75 cc. per kg., administered by intraperitoneal injection) were used in all experiments. One or both cerebral hemispheres were widely exposed. The pial vessels were observed with a compound microscope. The beam of light directed to the surface of the hemisphere was filtered through an ammoniacal copper sulphate solution, in order to remove heat rays and provide better color contrasts.

The stimulating electrodes—fine silver wires, with a small bead at the tip—were applied to the pial surface. The interelectrodal distance was about 1.5 mm. The stimuli were "tetanizing" shocks from a Harvard induction coil, delivered for a period of 3 to 5 seconds. The stimulation was always below threshold for the production of any immediate cortical electrical "after-discharge." Mechanical stimulation was obtained by means of a few light touches with a small glass rod. These stimuli caused only a slight compression of the tissues, without any visible structural damage. A six-channel Grass ink-writing oscillograph was used for the study of the cortical electrical activity (8).

RESULTS

The arteries and veins of the pia are readily identifiable. Besides distinctive features in their course and manner of branching, their difference in color is very striking—the arteries are a bright scarlet, the veins a purplish red. The blood flow in the arteries is ordinarily too rapid to be followed, but in the veins it is clearly visible. The entire picture of the pial circulation is markedly changed when, following stimulation, depression of activity spreads over the cortex.

1. At the stimulated region, as the electrical activity becomes progressively more and more depressed, a very conspicuous dilatation of the arteries occurs. In the veins, the rate of flow is strikingly increased, and these vessels

promptly become as scarlet as the arteries. Many small vessels, unnoticeable before, become clearly outlined in the field.

From the stimulated region similar changes spread out slowly in all directions. This spread is strictly analogous to that of the depression of the electrical activity, and the two processes appear coincidentally at any given region. That is, the wave of vasodilatation and increased blood flow successively affects adjacent areas and within about 3 to 6 minutes involves all of the dorsolateral aspect of the cerebral hemisphere of the rabbit. As in the case of the depression of the cortical potentials, the only area not involved is a small region medial to the parasagittal sulcus. This area corresponds to the cytoarchitectonic area "retrosplenialis granularis dorsalis" (Rsg β) of Rose (11).

At any given region, maximal dilatation of the arteries is reached in about 0.5 to 1.5 minutes after it first becomes noticeable. The gradual subsidence

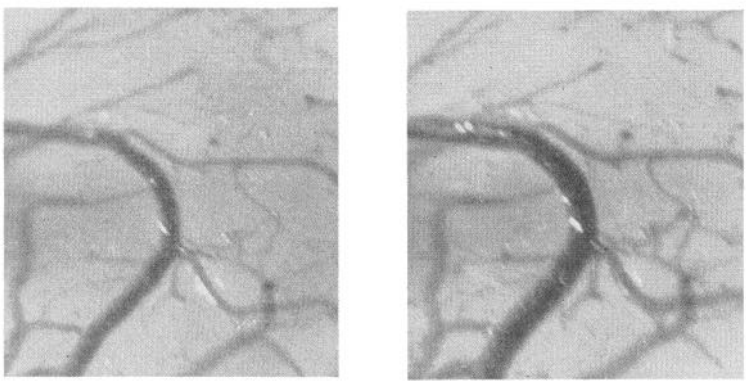

FIG. 1. A. Control before stimulation. The large vessel is an artery, of about 120μ diameter. B. The wave of depression has reached the region (see Fig. 2). The diameter of the artery is approximately doubled.

is somewhat more variable in time. As a rule, however, within 1.5 to 3 minutes the caliber of the arteries has returned to previous values. Arteries of all sizes are strongly dilated. The increases in diameter, as observed with the microscope, are of the order of 50 to 100 per cent (Fig. 1). Although precise measurements with an ocular micrometer are difficult to make, due to the pulsations of the exposed hemisphere (chiefly those caused by the respiration), the curve of Fig. 2 illustrates the general course of a representative observation.

Occasionally, the period of marked dilatation was followed, in some arteries, by a long period of a relatively much slighter reduction of caliber. The change in the pial circulation was in most cases easily perceived with the naked eye, as a widening area of a reddish color.

2. With minimal effective stimuli, the wave of vasodilatation, like the depression of activity, spreads only in the stimulated hemisphere. No change takes place in the pial circulation of the opposite hemisphere while the wave of vasodilatation is spreading over the stimulated side.

If, following supraminimal stimulation, a depression of activity appears in the opposite hemisphere, then vasodilatation and increased blood flow also occur in that hemisphere. The changes in the pial circulation are first seen at the region symmetrical to the one stimulated, and spread out from there to the rest of the hemisphere in exactly the same manner as described for the stimulated side. The latency for the appearance of the depression of activity, and the concomitant changes in the pial circulation, at the symmetrical region is longer than at the stimulated region, so that the spreads in the two hemispheres are not coincident. The response on the opposite side, starting a little later, as a rule covered at any given time a smaller area than that involved on the stimulated side. The changes in the pial circulation are similar in a given region, whether the stimuli have been applied near or far, and regardless of the region stimulated.

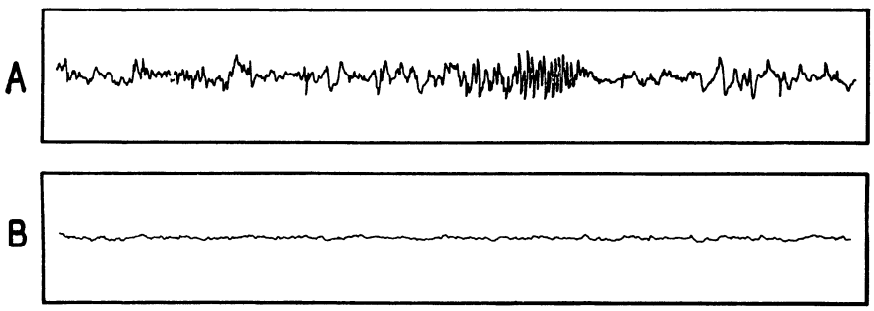

FIG. 2. Electrograms taken from electrodes in the immediate neighborhood of the area shown in Fig. 1. A. Control, before stimulation. B. The depression of electrical activity, taken during the exposure of Fig. 1B.

3. Specific electrical activity, clearly different from the "spontaneous," often appears during the depression of cortical activity. This activity is of a "convulsive" character, and when intense closely resembles the "seizure pattern" of experimental epilepsy, (8). The response of the pial vessels is similar whether pure depression of the spontaneous electrical activity takes place or whether specific increased activity of any intensity develops during the depression.

4. In many experiments, the systemic arterial pressure was recorded while observations were made on the pial circulation and on the electrical activity of the cortex. One carotid was cannulated and connected to a membrane manometer. No change of the blood pressure took place while the cortex was stimulated and the wave of vasodilatation and increased blood flow spread over the hemispheres.

COMMENT

The factors regulating the blood flow in the brain have been reviewed recently by Forbes (3), who tabulated the extracerebral and the cerebral factors. In the phenomenon observed in the present experiments, the changes in

caliber of the cerebral arteries seem to be active and correlated with local activity of neurons. That the vascular reaction is secondary to a local change in the activity of nervous elements is indicated by the cases in which depression of activity is elicited in the opposite hemisphere. Arterial vasodilatation and increased blood flow then appear at the region symmetrical to that stimulated. Only nervous pathways could establish this solidarity between symmetrical cortical regions in the two hemispheres. General factors are excluded by the fact that there were no changes in the systemic arterial pressure during the spread of the response.

It seems clear, therefore, that the change in the activity of the cortical neurons, when depression is starting in any given region, causes local vaso-

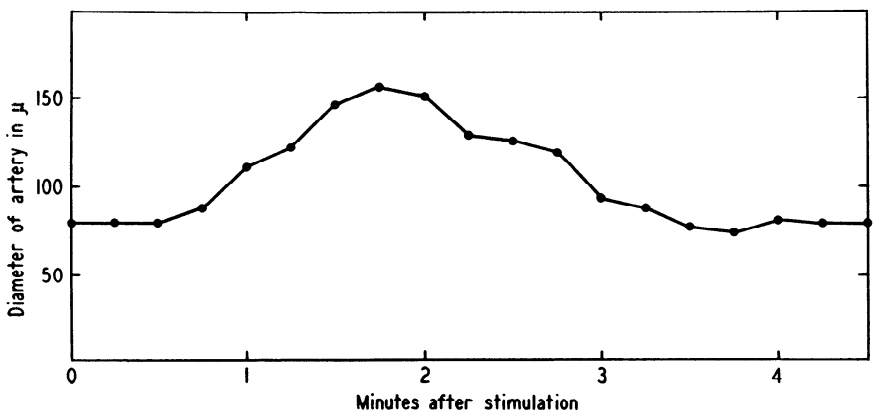

FIG. 3. Graph showing the time course and magnitude of arterial vasodilatation attending a depression.

dilatation and increased blood flow. An understanding of the inter-relations between the two phenomena awaits further investigation. The following surmises may be suggested. A chemical vasodilator agent might be released into the interstitial fluid: this is the most likely mechanism by which the response of the vessels might be produced. Another possibility would be a local, intrinsic system of vasomotor nerves. No evidence has ever been found of such a system, but the prompt and marked dilatation of large pial arteries that was observed in the present experiments might suggest this possibility.

Among the vasodilator substances, carbon dioxide is of special importance. That it is a powerful cerebral vasodilator has been established by several authors, and with different methods (5, 15, 1, 13). Regional increases in blood flow correlated with local neuronal activity, and probably caused by increased cellular metabolism with a corresponding rise in CO_2 tension, have also been reported by several authors (14, 13, 12). Since the vasodilatation observed in the present experiments develops as the electrical signs of neuronal activity wane, a correlation with a rise in CO_2 tension is not probable. Although some cortical elements are probably active in bringing forth

the spread of the response, the majority of the cells show a depressed activity, *i.e.*, they probably produce less CO_2, so that a rise sufficient to cause the conspicuous dilatation observed is doubtful. As an additional argument it may be mentioned that in many experiments the small veins were carefully observed in order to find out whether they became darker before they turned as bright scarlet as the arteries. No such darkening was seen. Although the vessels of the brain are highly sensitive to CO_2, this agent would act mainly on the fine, readily permeable vessels. A large concentration would be necessary to produce the marked dilatation of large arteries seen here. Such high concentration would presumably be associated with high O_2 consumption. Some darkening of the blood would, therefore, be expected to appear before the period of vasodilatation.

Some other metabolite, *e.g.*, a fixed acid, or a change in concentration of some inorganic ion, or some specific organic compound, might be the agent for the vascular reaction observed. Whatever the mechanism of the vasodilatation, it is to be expected that the marked increase in flow will in turn influence the activity of the cortical neurons in the region concerned (for instance, by producing acapnia, and so altering the functional activity of the cortex). The time course of the depression of activity in a given region is therefore probably influenced by the vascular reaction.

The cerebral blood flow during seizures induced by electrical stimulation has been studied by many investigators (4, 10, 2, 7) by means of thermocouples. Penfield (9) observed the pial arteries in epileptic patients during craniotomy. These authors report an increase of flow in the portion of the cerebral cortex involved in the convulsive discharge. Gibbs, Lennox and Gibbs (6) measured the jugular flow in epileptics and found also an increase accompanying seizures. In the present experiments, vasodilatation and increased flow always occurred in any cortical region when a wave of spreading depression of activity reached it. This increase occurred whether there was pure depression, or whether convulsive potentials appeared. Hence, the increased flow cannot be attributed to the increased neuronal activity of the discharge itself. The vascular reaction is correlated with the mechanism of depression and its spread, and in our experiments precedes the convulsive potentials that often occur in depressed areas.

The close relations between the spreading depression and the discharges of experimental epilepsy have been discussed by Leão (8).

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Summary

In rabbits, under dial narcosis, a wave of marked dilatation of and increased blood flow in the pial vessels travels over the cerebral hemispheres concomitantly with the depression of electrical activity that is elicited by weak electrical or mechanical stimulation of the cerebral cortex. The two

processes appear coincidentally at any given region, and involve all of the dorsolateral aspect of the hemisphere, with the exception of a small region, medial to the parasagittal sulcus (area Rsg β, of Rose).

Arteries of all sizes are greatly dilated. The increases in diameter are of the order of 50 to 100 per cent. The flow in the veins is strikingly increased and these vessels promptly become as scarlet as the arteries.

The changes in the pial circulation are similar whether only depression of the spontaneous electrical activity takes place or whether "convulsive" activity, of any intensity, develops during the depression.

The vascular response is apparently secondary to a local change in the activity of nervous elements. Whatever the mechanism of the vasodilation, the marked increase in blood flow probably influences in turn the activity of the cortical neurons.

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