A POSSIBLE UTILIZATION OF NEURONALLY ISOLATED CEREBRAL CORTEX FOR THE STUDY OF THE MODE OF ACTION OF DRUGS IN A LONG-TERM EXPERIMENT

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The methods utilized by pharmacologists for the study of the sensitivity to drugs of one or other part of the central nervous system include the operation for neuronal isolation of brain tissue. This measure effectively excludes the nervous connections of various centers or regions of the brain or spinal cord, and so makes it possible in some measure to determine whether or not there is any direct or indirect action of the substance on the isolated structure. The operations include division of the brain stem at the intercollicular level, or between the medulla and the spinal cord [3-5]; alternatively a small area of cortical tissue [6, 9] or extensive regions of the cortex may be isolated [10]. However, these operations are all subject to serious shortcomings associated with difficulty in the analysis of the results obtained. Thus pharmacological investigations on animals with a divided brain stem and most of the investigations on animals with an isolated strip of cerebral cortex have been carried out in acute experiments so that inevitably the application of the findings to normal animals has been in doubt. It is true that a great deal of work on the isolated cortex has been carried out on chronic preparations [7, 8], but as has already been pointed out such an operation isolates a very small cortical area (usually a few square millimeters). This means that the electrodes recording electrical activity from such a strip must be placed very close to the point of operative interference—no more than a few millimeters away from the incision; then, through the formation of disintegration products and cicatrization damage is caused to the cortex not only at the time the incision is made, but also subsequently. These factors undoubtedly influence the sensitivity of the cortical cells to drugs. The same thing is true of the studies made by Rinaldi and Himwich, in their acute experiments.

In 1954 we developed a method of neuronal isolation of the whole of the neocortex; by this means we were able to continue observations on the operated animals for several months [1, 2]. The operation consisted in a division of all the pathways connecting the neocortex to the subcortical structures and to the paleocortex. Because at a certain point the corona radiata is concentrated into a compact bundle and occupies only a small area, its division at its most compact part, and division of the pathways connecting the hippocampus and fornix with the cortex is achieved by neuronal isolation of the neocortex. The approach to the corona radiata is made through the anterior portion of the splenial gyrus, which is incised longitudinally over a length of 1.5-2 cm. The incision is then made deeper by means of two spatulas until it extends as far as the lateral ventricle. Through this "window" the dorsal part of the gleaming white hippocampus is clearly visible. The division is made from outside and runs along the hippocampus whose lateral edge lies over the corona radiata close to the thalamus. The operation has been described in detail previously [2].

An important feature of the operation is that the pial circulation of the cerebral hemispheres remains intact. In our view such a preparation may be widely used for a detailed study of the influence of drugs on cortical electrical activity, i.e., for a study of the mode of action of substances on the cerebral hemispheres. Because animals operated on in this way survive for a long time opportunity is provided for a study of the action of various substances on the same animal.

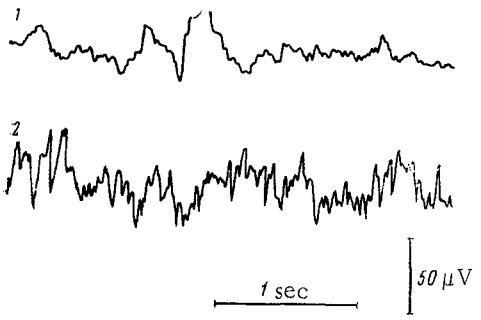

Fig. 1

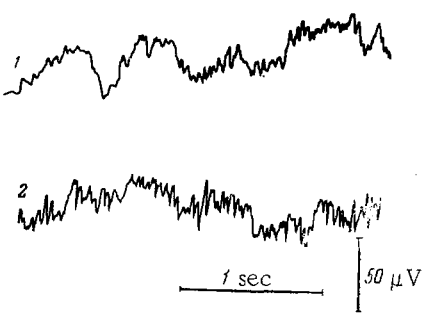

Fig. 2

Fig. 1. Electrical activity of (1) a neuronally isolated and (2) a normal feline cortex recorded 9 days after the operation and before the injection of caffeine. Bipolar leads. "Al'var" ink-writing oscillograph.

Fig. 2. Electrical activity of (1) the neuronally isolated and (2) the normal cortex of the same cat made 23 min after the injection of 240 mg/kg caffeine. The isolated cortex shows the appearance of rapid bursts of oscillations.

As histological studies of the operated animals have shown the neuronally isolated cortex of the cerebral hemispheres retains its 6-layered structure, even for many months after the operation. The chief structural changes occur in the 4th layer where certain of the cellular elements fail to survive.

We have studied the influence of various drugs on the electrical activity of a portion of cerebral cortex isolated in this way, and for this purpose we have made use of cats in which the isolation was made either unilaterally or bilaterally. In the former case, in addition to carrying out the isolation as described, we also divided the transverse commissural connections.

As an example in Figs. 1 and 2 we show a record of the cortical electrical activity from an operated cortex and from a normal cortex of the opposite hemisphere before and after intramuscular injection of caffeine. Even by the 4th day after the operation caffeine acts directly on the cortex, as it is usually held to do, and exerts a typical desynchronizing influence not only on the normal but also on the isolated cortex. In the latter case its influence must essentially be direct, and must be mediated humorally. This result confirms the general view of the direct action of caffeine on the cerebral cortex.

Nembutal however, whose chief action is subcortical does not influence the electrical activity of the isolated cortex, but greatly influences the activity of the "normal" hemisphere.

In the two examples given we deliberately used substances whose mechanism of action had been well studied; the results obtained on the preparation with the isolated cortex confirm the generally held view concerning the action of these drugs.

What we have said allows us to conclude that the method of neuronal isolation of the cortex in a chronic preparation may be used for a study of the mode of action of drugs.

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