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The Recovery of the Electrocorticogram of Normothermic Canine Brains after Complete Cerebral Ischemia

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SUMMARY. Complete cerebral ischaemias of 1 to 30 min duration were performed under normothermic conditions in completely isolated canine heads perfused from a donor dog. The electrocorticogram was found to return in the reperfusion period following these complete ischaemias. The latency of recovery, i. e. the interval between the end of the complete cerebral ischaemia and the reappearance of the first cortical potentials, increased with increasing duration of the complete cerebral ischaemia; thus, the latency of recovery after a complete ischaemia of 30 min amounted to 11 to 12 hours.

KEY WORDS: Cerebral Ischaemia - Anoxia - Electrocorticogram - Postischaemic Recovery.

ZUSAMMENFASSUNG. Komplette Gehirnischämien von 1 bis 30 min Dauer wurden in Normothermie an isolierten Hundeköpfen gesetzt, die von einem Spendertier durchblutet wurden. Spontane Cortexpotentiale kehrten nach diesen kompletten Gehirnischämien wieder. Die Erholungslatenz, d. h. die Zeit vom Ende der kompletten Gehirnischämie bis zur Wiederkehr der ersten spontanen Cortexpotentiale, wurde mit zunehmender Dauer der kompletten Gehirnischämie länger. Die Erholungslatenz betrug nach 30 min langer kompletter Gehirnischämie 11 bis 12 Stunden.

SCHLÜSSELWÖRTER: Cerebrale Ischämie - Gehirnanoxie - Electrocorticogramm - Postischämische Erholungszeit.

In earlier experiments (9) it could be demonstrated that the first electrical activity of the cortex following a 25 min complete cerebral ischaemia in normothermia reappeared spontaneously in the reperfusion period after a delay of 10 hours. Further investigations (2) have shown that following a 30 min complete ischaemia in normothermia the electrocorticogram could return after 7 to 8 hours. In contrast to these observations Hossmann & Sato have

found the first reappearance of an electrocorticogram 50 to 120 min following a 60 min interruption of the cerebral blood supply. The present experiments were designed to determine in normothermia 1. again the maximum duration of complete ischaemia after which the electrocorticogram reappears spontaneously and 2. the latencies of recovery of the electrocorticogram after various durations of complete ischaemia in the isolated dog's head.

MATERIAL AND METHODS

The experiments were performed on completely isolated canine heads which were perfused from a donor dog via PVC-tubings. These tubings connected the carotid arteries of the isolated head and the femoral artery of the donor dog (Fig. 1). The body weight of the animals from which the isolated heads were derived ranged between 3 and 8 kg, that of the donor dogs between 18 and 45 kg. The animals were anaesthetized with pentobarbital-sodium (Nembutal®) (25 mg/kg). The vertebral arteries of the isolated heads were ligated and the spinal artery was compressed by an inflatable balloon introduced into the vertebral canal. The venous blood dropping from the isolated head was collected in a funnel and returned to the donor dog by a sigmamotor pump. The blood in the funnel was filtered through pyrex glass wool in order to eliminate platelet aggregates occurring (7). The perfusion pressure in the anastomosis was maintained constant at 100 mm Hg by a throttle. The temperature of the isolated brain measured with thermistor probes which were located between dura and scull was maintained at 37 ±

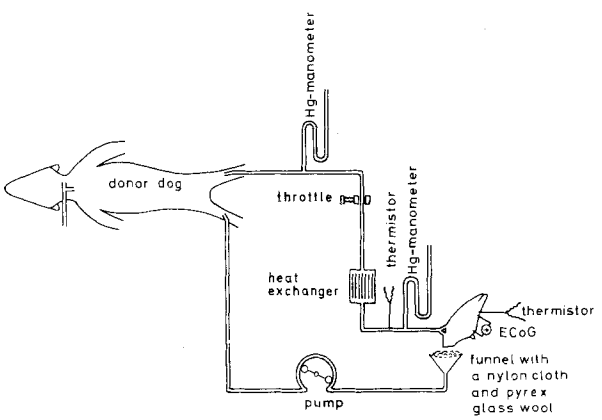

Fig. 1. Schematic representation of the perfusion system of the isolated canine head

0.15°C throughout the whole experiment. The experiments were conducted at a room temperature of 34°C. During the time of perfusion the arterial blood in the PVC-tubings was warmed up to 37°C by passing a water heat exchanger. During the time of complete ischaemia the isolated head was heated additionally using a hot air fan. Blood coagulation was prevented by administration of Vetren® (20 mg/kg = 2900 I. U. Heparin-Na) dissolved in Ringer's solution. The donor dogs relaxated by repeated i. v. injections of suxamethonium (Succinyl-Asta®, 2 ml every 2 to 3 hours) were ventilated artificially (Engstrøm-Respirator, LKB Medical AB, Brommar, Sweden) with a gas mixture of room air and oxygen (oxygen content 30-35%). The anesthesia was maintained by repeated administration of Nembutal® (2 mg/kg) every 3 to 4 hours. The electrocorticogram of the isolated head was recorded (EEG-Recorder Schwarzer, München and Alsfeld/Leine) unior bipolarly using silver electrodes screwed into the scull.

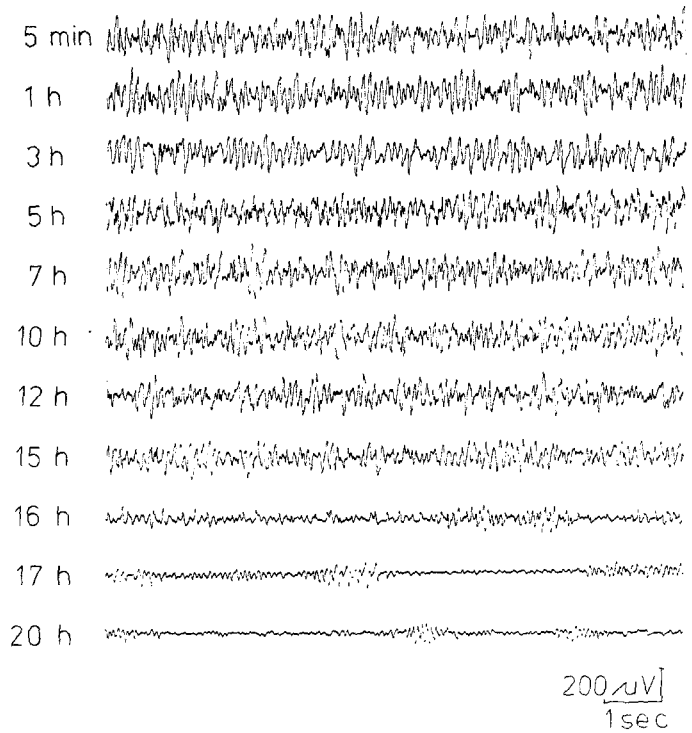

Fig. 2. Electrocorticogram of the isolated head in normothermia at several times (5 min to 20 hrs) after connection of the isolated head with the circulation of a donor dog

Earlier experiments could demonstrate that the O_2-uptake of the brain (3) as well as the concentrations of cortical high energy phosphates and carbohydrates (2) of the isolated head are comparable to those of a dog's head in situ. However, the duration of the survival time of the isolated head proved to be limitated. As can be taken from Fig. 2 the electrocorticogram of the isolated brain remains unchanged only for an average duration of 12 to 14 hrs under normal perfusion conditions.

Complete ischaemias were performed on a total of 40 isolated canine heads by occluding the anastomosis between the femoral artery of the donor dog and the carotid arteries of the isolated head. After connection of the isolated head to the circulation of the donor dog, the viability of the isolated brain was tested by a 1 min complete ischaemia. The latency of recovery of the electrocorticogram was not allowed to last more than 25 sec after a complete cerebral ischaemia of 1 min; prolonged latencies of recovery are indicative of a cerebral damage which possibly took place during the surgical preparation. Therefore two experiments with a latency of recovery longer than 25 sec had to be discarded. After an interval of 30 min the 1 min complete ischaemia in all cases was followed by a second complete ischaemia. The duration of this second ischaemia amounted to 3, 5, 8, 10, 12, 15, 17, 20, 25, or 30 min. Thus, each isolated dog's head had two complete ischaemias. After the end of the second complete ischaemia the electrical activity of the cortex was recorded for 20 hrs.

As latency of recovery of the electrocorticogram the interval was determined between the end of a complete ischaemia and the reappearance of the first cortical potentials measurable with a minimum amplitude of 10 μV and 50 μV.

RESULTS

Fig. 3 gives the results from the experiments described. This figure indicates that the latency of recovery of the electrocorticogram is directly correlated with the duration of the complete ischaemia. In 3 from 5 experiments with an ischaemia of 25 min 10 μV potentials of the cortex could be observed after a reperfusion time of 9, 10, and 10.5 hrs, respectively. No potentials with an amplitude of 50 μV could be recorded in these experiments although the reperfusion time in all cases exceeded 20 hrs; the maximum amplitudes of these electrocorticograms extended to only 40 μV. In the remaining 2 experiments with a 25 min ischaemia a spontaneous recovery of cortical activity was found to fail totally. After a complete cerebral ischaemia of 30 min duration only in 2 out of 5 experiments cortical potentials of 10 μV amplitude were found; the latency of recovery for these potentials amounted to 11 and 12 hrs, respectively. The potentials in these experiments reached a maximum amplitude of 20 μV only.

In Fig. 4 and 5 representative examples of original registrations from 2 experiments are given. The first curve in each figure represents an electrocorticogram recorded during the control period. In Fig. 4 the curves 2 to 6 give recordings of the cortical activity following an 8 min ischaemia regi-

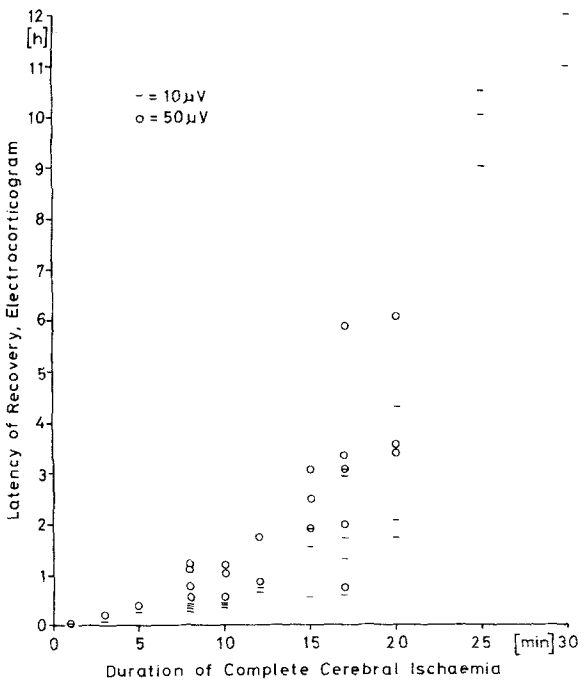

Fig. 3. Latencies of recovery of the electrocorticogram, i. e. interval between the end of the complete ischaemia and the first reappearance of cortical potentials of 10 μV (-) and 50 μV (o) at various durations of complete ischaemia of the brain in normothermia. In the reperfusion period of the 25 and 30 min ischaemias 50 μV potentials could not be observed. The data of the 1 min (n = 38), 3 min (n = 4) and 5 min (n = 4) ischaemias represent mean values; all other values plotted are single measurements

stered at several times in the reperfusion period. From this figure it is obvious that first 10 μV potentials appearing spontaneously could be observed 20 min after the end of the ischaemia; in the fourth hour of this reperfusion period the electrocorticogram almost had returned to its control configuration.

When the perfusion of the isolated head was stopped for 20 min, recovery of the electrocorticogram was only incomplete, as Fig. 5 indicates. In this experiment the first spontaneous potentials with an amplitude of 10 μV were found to return 2 hrs after the end of the ischaemia. Even after a reperfusion period of 20 hrs the recovery of the electrocorticogram did not exceed that one which is shown in the figure for a duration of perfusion of 7 hrs.

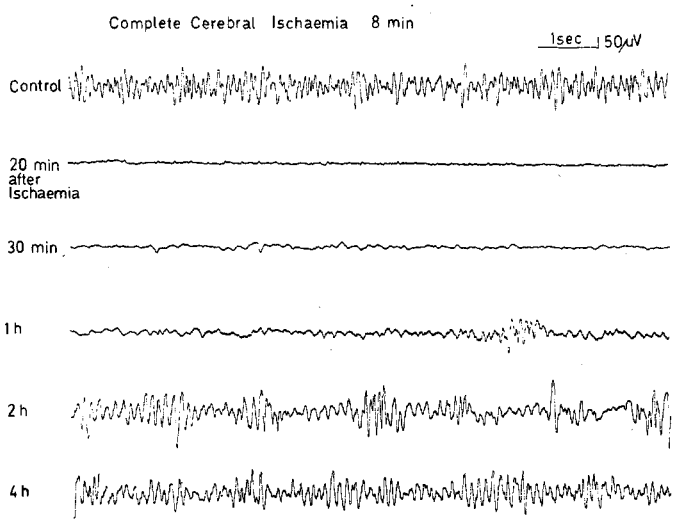

Fig. 4. Electrocorticogram before (Control) and at various times after a complete cerebral ischaemia of 8 min duration in normothermia. Unipolar recording, occipital

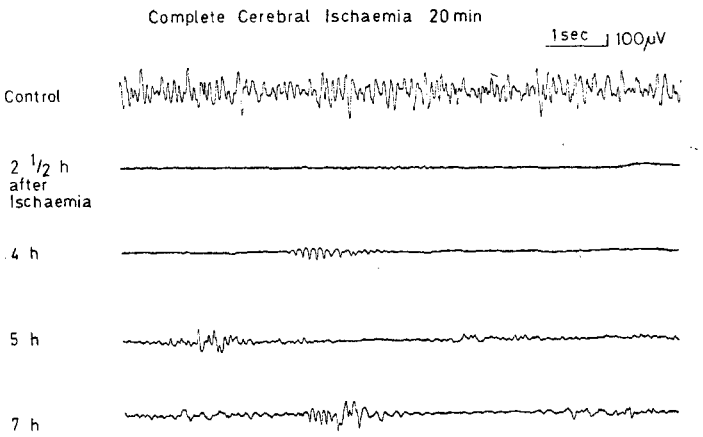

Fig. 5. Electrocorticogram before (Control) and at various times after a complete cerebral ischaemia of 20 min duration in normothermia. Unipolar recording, occipital

DISCUSSION

Experiments described earlier (4) demonstrated that a complete recovery of all cerebral functions in normothermia only could be observed if the complete ischaemia of the isolated canine head did not exceed a maximum duration of 8 to 10 min. On the basis of these results a recovery observable after a complete ischaemia of more than 10 min duration consequently must be incomplete and only temporary.

Further investigations (9) showed that a complete ischaemia of 25 min is the maximum duration after which potentials of the cortex reappear spontaneously in normothermia. The present data, however, demonstrate that these potentials also can be found after a 30 min ischaemia in 2 out of 5 experiments. This only can be explained by our increased experimental experience resulting in the decreased duration of surgical preparation of the animals and a more careful operation procedure. Now, the latency of recovery of the first 10 μV potentials of the cortex following a 30 min complete ischaemia ranged between 11 and 12 hours. In experiments designed to investigate the content of high energy phosphates and carbohydrates in the tissue of the brain after 30 and 60 min ischaemia in normothermia (2) the latency of recovery was found to amount only to 7 to 8 hrs. This shorter duration of recovery must be assumed to depend upon an increase in irritability following the repeated local application of strychnine in these investigations; it also could be due to the decreased depth of narcosis during the course of those experiments.

Following a total clamping of both venae cavae and the ascending aorta in dogs for a duration of 20 min Yashon et al. registered first cortical potentials with a maximum amplitude of nearly 50 μV reappearing after 5 hrs of reperfusion. This latency of recovery is in good accordance to the present results.

Hossmann & Sato described spontaneous cortical potentials returning already 50-120 min after cerebral ischaemias of 1 hr duration. The marked difference between these data and the results described only can be explained by the different experimental procedures employed. Whereas in our experiments the temperature of the brain was maintained at 37°C even during the complete ischaemia this obviously was not the case in the experiments reported by Hossmann & Sato. In their experiments the temperature may have dropped during the ischaemia. Unpublished data with the isolated head have shown that under the conditions of normal room temperature the temperature of the brain decreased from 37°C down to 30°C during an interruption of cerebral blood supply of 30 min duration. At the end of an 60 min ischaemia the temperature of the brain was found to drop down to 28°C. Thus, one can suppose that in the experiments reported by Hossmann & Sato the temperature of the cat's brain also had decreased in a comparable extent. A decrease of cerebral temperature during the complete ischaemia will, however, reduce the susceptibility of the brain for anoxia. From earlier investigations we know that the latency of recovery is reduced in hypothermia (5). In addition the depth of anaesthesia may provide another explanation for the discrepancies between our results and the data of Hossmann & Sato. In our experiment pentobarbital-sodium was injected every 3-4 hrs; a correspond-

ing procedure is not described in the publication of Hossmann & Sato. Furthermore in the experiments of Hossmann & Sato ischaemia was produced by the total clamping of the left internal mammilary artery, the innominate artery, and the right subclavian artery; additionally, the arterial blood pressure was decreased by the administration of Arfonad ®. Nevertheless it cannot entirely be excluded that a small amount of blood perfusion still persisted in some of these experiments. This remaining minimum blood flow could be assumed to prolong the maximum duration of tolerance against an O_2-deficiency. One of the advantages using the isolated head technique is that the total clamping of the inflow cannula must always produce a complete ischaemia of the brain.

The short latencies of recovery found in these experiments after complete ischaemias of 15 to 17 min (Fig. 3) can be explained by the age (1 to 1.5 years) of the animals used. After a test ischaemia of 1 min the brains of these dogs showed a latency of recovery of only 15 sec, whereas the latency of recovery of these test ischaemias was 25 sec on average. This decrease of the latency of recovery is indicative of the higher tolerance of young brains against anoxia. Longer latencies of recovery after complete ischaemias of 15 and 17 min duration were found in adult dogs of approximately 4-5 years of age. The remaining experiments with ischaemias of a duration of 1 to 12 and 20 to 30 min were performed on isolated heads derived from adult dogs of an age of approximately 4 to 5 years. These brains had shown normal latencies of recovery of the electrocorticogram after the preceeding 1 min test ischaemia.

On the other side the surgical procedure isolating the canine head may have led to a damage of the brain which hardly can be determined quantitavely. This damage also may have influenced the results of our experiments. In some experiments the development of cerebral edema after the complete ischaemia resulted in a prolongation of the latency of recovery. Probably this was the case especially after the longer ischaemias.

As can be seen from the electrocorticograms given in Fig. 4 and 5 it appears impossible to make a prediction on the further recovery of the brain from one recording of an electrocorticogram only. For instance the electrocorticogram recorded 1 hr after a complete 8 min ischaemia shows a confirmation comparable to that recorded 7 hrs after a 20 min complete ischaemia. 4 hrs after a complete 8 min ischaemia the electrocorticogram had nearly returned to its control configuration, whereas at a comparable time after a complete 20 min ischaemia only bursts of 8 to 10 per second activity were observed. Even the complete recovery of the electrocorticogram found approximately 20 hrs after a complete 8 min ischaemia does not allow any prediction on the complete recovery of the entire integrative cerebral function, since neurological defects can only be studied in longterm experiments with intact animals.

The recovery of the electrocorticogram must be distinguished from the recovery of other electrical potentials of the brain. The latency of recovery of the electrocorticogram needs significantly more time than the recovery of the acetylcholine- and strychnine-spikes (10), the dc-potentials (6) or the pyramidal response following electrical stimulation (8). Experiments with the isolated canine head have demonstrated that during recovery the cerebral phospholipids (1) as well as the high energy phosphates and carbohydrates (2)

were rapidly and totally restored to their control values after a complete ischaemia of 30 min duration. After a 60 min ischaemia the metabolic recovery of the brain was found to be only incomplete after a reperfusion time of 8 hrs. The partial restitution of the cerebral metabolic state after a complete 60 min ischaemia combined with the absence of recovery of the electrocorticogram, the total recovery of the acetylcholine- and strychnine-spikes, and the normal reaction of the dc-potentials of the cortex indicates that there is no correlation between electrical activity and biochemical data.

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