EFFECT OF HYPERCAPNIA ON THE SPONTANEOUS AND EVOKED POTENTIALS IN THE INTACT AND ISOLATED CEREBRAL CORTEX IN RABBITS

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Recent researches into the effect of carbon dioxide on the central and peripheral nervous system have demonstrated the important role of this physiological metabolite in the regulation of the fundamental nervous processes [4,5,7,9,10]. Inhalation of a mixture of 30% CO_2 with oxygen has found application outside the Soviet Union in the treatment of neuroses [10]. Dell and co-workers [5,7] have postulated a specific stimulating action of carbon dioxide on the activating system of the brain stem. In our previous investigations we showed that whereas the inhalation of weak concentrations of CO_2 (less than 10%) was followed more especially by signs of desynchronization of the EEG, the inhalation of concentrations greater than 10% led to marked depression of the EEG (associated with a high blood pressure but not with signs of hypoxemia), independent of the tone of the reticular formation of the brain stem and apparently reflecting a direct depressant action of carbon dioxide on the cells of the central nervous system. The direct sensitivity of the cortex to weak, desynchronizing concentrations of carbon dioxide was demonstrated by Yu. N. Ivanov [1].

We have studied the effect of hypercapnia on the spontaneous activity and evoked potentials in areas of the cortex isolated by division of all their nervous connections, and also the action of carbon dioxide on the local paroxysmal discharges of the brain and on the nonspecific thalamo-cortical "recruiting rhythm."

EXPERIMENTAL METHOD

Experiments were conducted on 42 rabbits weighbing 2.5-3.0 kg, lightly premedicated with nembutal or without nembutal. The brain was exposed under ether anesthesia. The rabbits were fixed in a stereotaxic apparatus. Electrocorticograms were recorded from bipolar chloride-silver button electrodes, the inter-electrode distance being 1-2 cm. Electrical stimulation was applied to the subcortical regions by means of a rectangular pulse generator through bipolar concentric electrodes, oriented in relation to the stereotaxic coordinates of Sawyer et al. [12]. An area of the hemisphere with an area of 15 × 20 mm and a thickness of 3-5 mm was isolated by the method of Burns [6] and Ingvar [8]. Local paroxysmal discharges were evoked in the cortex by application of filter paper (2 × 2 mm) soaked in solutions of camphor or strychnine. A "recruiting rhythm" was evoked by stimulation of the intralaminar nuclei of the thalamus with pulses at a frequency of 6-20/sec. The EEG was recorded on a four-channel ink-writing electroencephalograph with a linear characteristic of up to 70-80 cps. The animals inhaled the gas mixtures from bags through a tracheotomy cannula fitted with a valve, and exhaled into the atmosphere.

EXPERIMENTAL RESULTS

In the first series of experiments (15 rabbits) the effect of hypercapnia (5-30% CO_2 with 25-70% O_2) was studied on the spontaneous activity and electrically evoked paroxysmal potentials in the isolated area of the cortex, connected with the rest of the brain only through the pial vessels.

It will be seen from Fig. 1 that the spontaneous activity of the isolated area differed sharply from the activity of the symmetrically opposite intact cortex. The activity of the latter presented the usual picture of irregular waves with an amplitude of up to 150-200 μV and a frequency of 1-4/sec, on which were superimposed faster waves of lower amplitude. In the isolated cortex, however, against a background of a general lowering of the level of activity, cycles of high-amplitude discharges (up to 500-600 μV) consisting of fast and slow waves periodically appeared. More

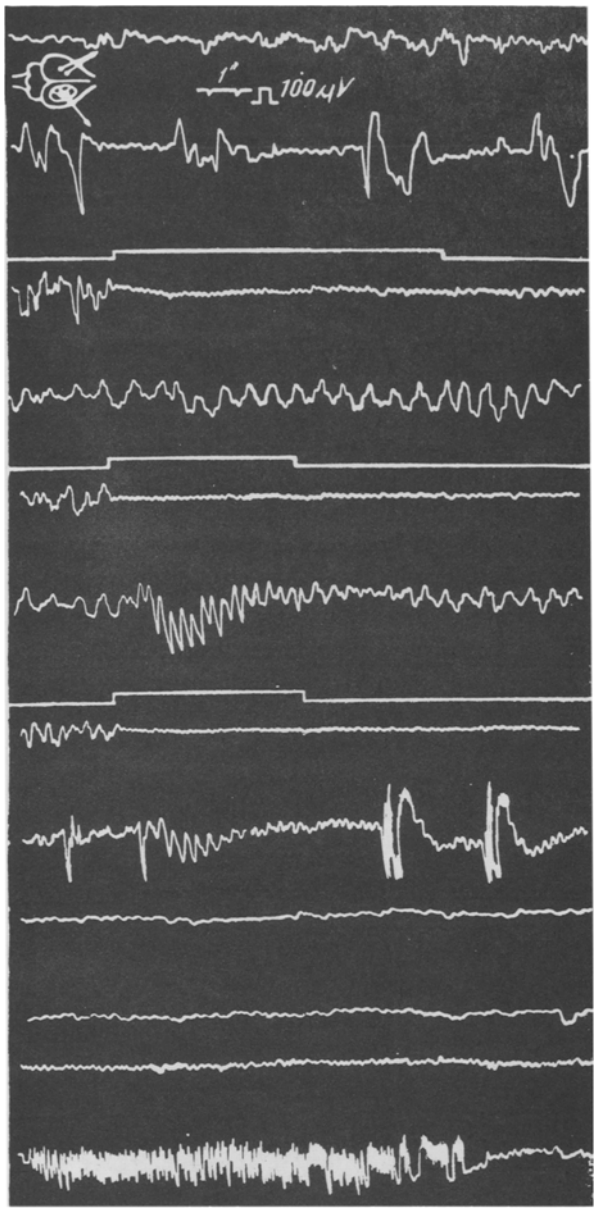

Fig. 1. Comparative effect of hypercapnia and electrical stimulation of the reticular formation of the midbrain on the EEG of the intact (upper tracings) and isolated (lower tracings) cerebral cortex in rabbits (pooled data from several experiments). a) Initial period; b,c,d) stimulation of the reticular formation of the midbrain (P_8, L_2, h_{14}); e) 1 min after beginning of inhalation of 20% CO_2 + 25.5% O_2; f) 2 min after changing to inhalation to air. Straight lines above EEG – marker of electrical stimulation (e-4 V, 120 imp/sec, 1 millisec).

rarely the EEG consisted on a continuous series of slow, high-amplitude waves (Fig. 1, b). Treatment of the isolated area with 96° alcohol, or mechanical destruction of the area abolished this activity, indicating that these potentials were local in origin. Peripheral stimuli (sound, electrical stimulation of the sciatic nerve) desynchronized the intact cortex but had no effect on the EEG of the isolated cortex. Nembutal, injected intravenously (10-20 mg/kg), gave rise to the development of high-amplitude spikes in the intact cortex and totally abolished the activity in the isolated area. These results correspond to those obtained by Ingvar from the isolated area of the cat's cortex. Stimulation of the reticular formation of the midbrain may affect the EEG of the isolated cortex by modifying the cortical blood flow [8]. In our experients the action of carbon dioxide was therefore compared with the effects of electrical stimulation of the reticular formation of the midbrain and of its chemical stimulation with adrenalin [5,7].

Adrenaline, injected intravenously (50 μg), gave rise to apnea and to marked desynchronization in the intact cortex, but caused no significant changes in the isolated cortex.

The types of the responses in the intact and isolated cortex during electrical stimulation of the reticular formation of the midbrain are shown in Fig. 1, b,c,d. With threshold and slightly over-threshold stimuli, causing prolonged desynchronization in the intact cortex, the EEG of the isolated area was hardly changed. With higher voltages, a series of high-amplitude discharges appeared in the isolated cortex during or after stimulation.

Inhalation of 5% carbon dioxide led to slight desynchronization of the intact cortex and to some increase in the frequency of the discharges in the isolated cortex, while 10% CO_2 caused a sharp fall in the amplitude of the EEG in the intact cortex and appreciable lowering of amplitude in the isolated area. At these concentrations the effect was more marked in the intact than in the isolated cortex. Inhalation of 20% carbon dioxide led to the almost complete disappearance of activity in both the intact and isolated cerebral hemispheres (Fig. 1, e). At these concentrations the blood pressure is slightly elevated while the HbO_2 concentration in the arterial blood remains normal [2,3].

After reverting to breathing normal air the initial EEG was quickly restored, although a typical paroxysmal activity (Fig. 1, f) frequently appeared in the isolated area, which was never observed in the intact cortex in these conditions. The increase in the voltage of the EEG over its initial level (what Yu. N. Ivanov calls the "recoil effect"), sometimes observed during the change from a brief period of hypercapnia, differs sharply from the changes described above. The experiments showed that before the typical paroxysmal activity could develop in the intact cortex, a much more prolonged period of deep hypercapnia was required (with 25% CO_2 - 24 h, with 40% CO_2 - about 6 h).

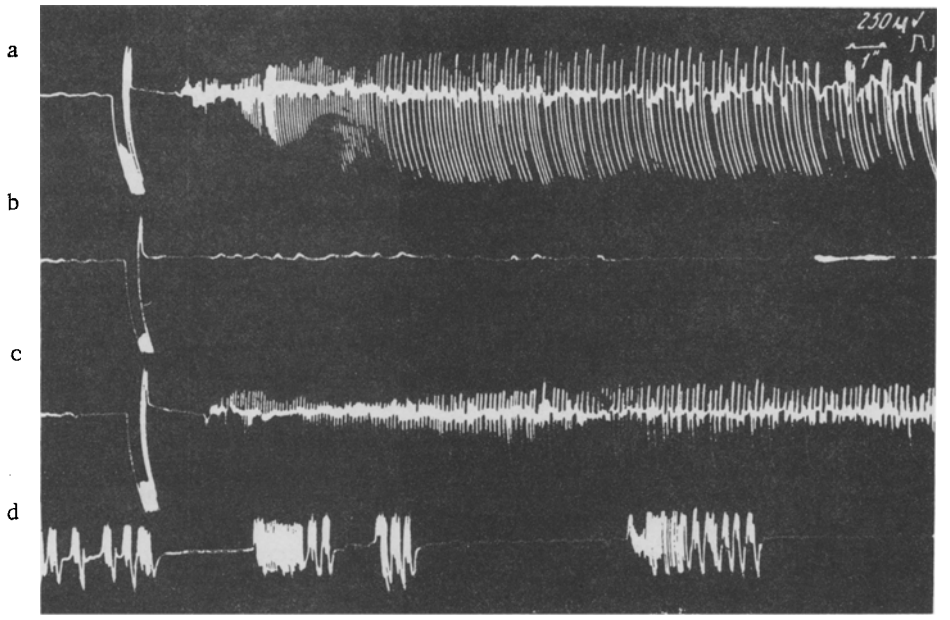

Fig. 2. Effect of hypercapnia on electrically invoked peroxysmal discharges in the isolated cerebral cortex. a) Initial period; b) 2 min after beginning of inhalation of 20% CO_2; c,d) 2 and 4 min after cessation of inhalation of CO_2; at the left side of a,b, and c) artifact from electrical stimulation (30 V, 10 imp/sec, 1 millisec). Recording electrodes situated 2 mm from stimulating electrodes.

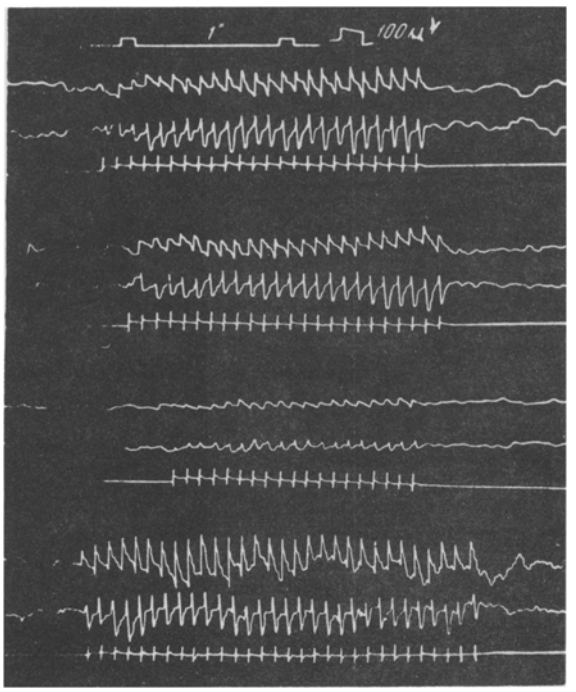

Fig. 3. Effect of hypercapnia on the "recruiting rhythm." a) Initial period; b) 2 min after beginning of inhalation of 10% CO_2; c) 2 min after beginning of inhalation of 20% CO_2; d) 1.5 min after resumption of air breathing. Significance of the curves (from above down): EEG of the left; EEG of the right parietal cortex; marker of stimulation of the N. parataenialis (5 V, 1 millisec).

After direct electrical stimulation of the isolated cortex for 1-2 sec a series of paroxysmal discharges lasting from 10 to 40 sec appeared (Fig. 2,a). Inhalation of 10% CO_2 had hardly any effect on the character of the paroxysmal activity, but 20% CO_2 abolished it completely (Fig. 2,b). From 1 to 2 min after the inhalation of carbon dioxide was discontinued, not only was the reaction restored, but the discharge became more prolonged, and when it was over repeated discharges often occured (Fig. 2,d).

In the second series of experiments (15 rabbits) the effect of hypercapnia was studied on the local paroxysmal discharges in the intact cortex after application of a 20% solution of camphor and a 0.1-1.0% solution of strychnine to part of its surface.

Paroxysmal activity developed in the treated area either in the form of a continuous series of successive discharges of a tetanic character or of less frequent, single, high-amplitude waves. In the symmetrically opposite area of the cerebral cortex no such changes in the EEG were observed. During inhalation of carbon dioxide, starting with a concentration of 10% (in some experiments, 5%), the camphor discharges disappeared completely. Reversion to breathing air not only restored the paroxysmal activity, but caused a slight increase in its amplitude over the initial level. The effect of 10-20% CO_2 on the paroxysmal potentials was also clearly demonstrated after the preliminary blocking of the reticular

formation of the midbrain with chlorpromazine (3 mg/kg), thus suggesting that the developing hypercapnic inhibition is extrareticular in nature.

In respect of the strychnine discharges (0.1-0.5% solution), inconstant results were obtained. In some experiments 10-20% CO_2 caused a sharp depression of these discharges, while in others the effect was insignificant even in a concentration of 30%. In all cases hypercapnia had no effect on the discharges caused by 1% strychnine.

In the third series of experiments the effect of hypercapnia was investigated on the "recruiting rhythm" caused by stimulation of the diffuse thalmic projection system [11]. The appearance of the "recruiting rhythm" in the ipsi- and contralateral parietal cortex after stimulation of the N. parataenialis is demonstrated in Fig. 3. An initial increase in the amplitude of the response may be seen in the cortex with each succeeding stimulating impulse. At threshold voltages the effect was more marked on the ipsilateral side, and as a rule it was absent in the frontal divisions of the hemispheres. If the position of the stimulating electrode was moved by 1-2 mm, the reaction disappeared.

Inhalation of 10-30% carbon dioxide suppressed the "recruiting rhythm" after 1-2 min. In some cases the action was clearly seen only with concentrations of 20% or higher, while in others the maximal effect was obtained with a concentration of only 10% of carbon dioxide. The degree of depression was more marked on the contralateral side. With the resumption of air breathing, stronger responses were frequently observed than in the initial period. Intravenously injected adrenalin (50 μg) in most cases had no effect on the "recruiting rhythm." Application of 0.1% strychnine to an area of the cortex caused a sharp increase in the amplitude of the recruitment response in that area without affecting the amplitude in the opposite hemisphere.

Moderate subnarcotic hypercapnia thus causes a sharp depression of both spontaneous and evoked potentials of the brain. This action is preserved in an isolated area of the cerebral cortex in the rabbit.

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