EFFECT OF FORMALDEHYDE ON CARBOHYDRATE METABOLISM OF THE BRAIN

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The writers showed previously that formaldehyde, in low concentrations, can depress the developmemt of essential changes in the ischemic heart [4, 6], and can also prolong the duration of cerebral ischemia compatible not only with the animals' survival, but also with subsequent restoration of their CNS functions [7, 8].

There have been several investigations of the effect of formaldehyde on metabolic processes in ischemic organs [2, 3, 5]. However, of the whole wide range of factors influencing it during ischemia, special attention must be paid to factors whose influence is not exerted through oxygen deficiency. Formaldehyde also is known to be a potentially toxic agent.

The aim of this investigation was to study some parameters of carbohydrate metabolism in the brain under the influence of formaldehyde in nonischemic dogs and to compare them with physiological parameters.

EXPERIMENTAL METHOD

Experiments were carried out on 12 mongrel dogs of both sexes, anesthetized with hexobarbital. A 0.2% solution of formaldehyde in a volume of 20 ml/kg body weight was injected into the carotid arteries of the animals at the rate of 10 ml/min. Dogs receiving intraarterial injections of a corresponding volume of physiological saline served as the control. Parameters obtained on intact animals were taken to be normal. The glucose concentration was determined in arterial and venous blood, for when the cerebral blood flow is disturbed this can give evidence of the intensity of biochemical processes; concentrations of lactate and pyruvate in the cerebrospinal fluid (CSF) also were determined and the ratio between them calculated. For these investigations cannulas were introduced into the right subclavian artery as far as the brachiocephalic trunk and into the right external jugular vein. The cisterna magna also was punctured. Parameters were measured in animals in the original state, immediately after injection of the solutions, and again 5, 20, 40, and 60 min later. The glucose concentration was determined by the glucose oxidase method [1]. Concentrations of lactate [9] and pyruvate [10] were determined by enzymic methods. Changes in the respiration rate (RR), blood pressure (BP), ECG in standard lead II, and the EEG in both parietal regions were studied. The EEG was recorded on a Type Eg-170 electroencephalograph (Sanei). The ECG, BP, and RR were recorded on a Biograph (Harvard Apparatus, USA).

The results were subjected to statistical analysis by the Fisher–Student method.

EXPERIMENTAL RESULTS

Immediately after injection of the formaldehyde solution the arteriovenous difference (AVD) for glucose fell by 45.5% to 3.0 ± 0.7 mg/100 ml blood (normal 5.5 ± 0.3 mg%), $P < 0.05$. After 5 min the AVD had fallen to 2.3 ± 0.2 mg glucose/100 ml blood. Starting from the 20th minute a gradual increase in AVD was observed, but it had not regained its original values by

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the end of the period of observation (73.2%).

Injection of formaldehyde did not cause statistically significant changes in the lactate concentration of the CSF. The increase in the lactic acid concentration was greatest at the time of injection and by the 20th minute of observation. Its value was 15.9 ± 1.3 and 16.0 0.9 mg%, respectively, equivalent to 115.7 and 116.7% of the normal value (13.7 ± 0.5 mg%). The lactic acid concentration then decreased, and by the end of observation it was indistinguishable from normal. However, the lactate/puruvate ratio increased by 20% ($P < 0.05$) and remained at this level until the 40th minute. Toward the end of observation the lactate/pyruvate ratio was completely back to normal.

Infusion of formaldehyde caused no statistically significant changes in BP, the heart rate (HR), or RR, although a tendency was noted for them to decrease. On the EEG high-frequency activity was inhibited and theta-waves predominated, with increased amplitude. The normal EEG was restored 20 min after injection of formaldehyde.

In experiments of the control group injection of physiological saline was not followed by changes in AVD for glucose until the 20th minute. A steady increase was then observed, and by the 20th and 40th minutes it was 6.0 ± 0.9 mg% glucose, or 108.7% compared with normal. By the 60th minute AVD was 30.6% higher than initially ($P < 0.05$). By this time the lactate/pyruvate ratio was higher than in the experimental series (111%) and than normally (107%).

Injection of physiological saline was not accompanied by changes in BP, HR, or RR. A gradual decrease of BP then took place, and by the 60th minute it was 77% of the initial value. Changes in HR and RR were not statistically significant. On the EEG beta- and alpha-activity disappeared and theta- and delta-waves predominated. The amplitude of the waves also was reduced. During the next 60 min the amplitude of the waves gradually increased, but the frequency characteristic of the EEG did not return completely to normal.

The experiments thus showed that the glucose consumption of the brain, recorded as the AVD, is significantly reduced after injection of formaldehyde and remained at a relatively low level for 60 min. This decrease in the rate of glucose assimilation is accompanied, however, by less marked pathochemical changes than in the control, for the lactate concentration in the CSF, at its highest, does not exceed the control value. Conversely, toward the end of observation a slight degree of metabolic acidosis was found in the control, whereas in the experiment the lactate and pyruvate levels and the ratio between them returned to normal, although glucose consumption remained depressed. The mild degree of activation of glycolysis by physiological saline and the regular rise of AVD for glucose which was observed evidently depended on the volume of fluid injected, producing excessive hemodilution and the development of hemic hypoxia. The physiological parameters also are evidence that the principal role in the development of adverse changes is played by the forced excessive volume of fluid, for depression of the EEG and the fall of BP were more marked than in the experiment.

The following conclusion can be drawn from an analysis of the experimental data:

1. The fall of AVD for glucose (glucose consumption) observed after intravascular injection of formaldehyde, while the cerebral blood flow was undisturbed and the lactate and pyruvate concentrations and the ratio between them quickly returned to normal, and functional changes were absent in the cardiovascular system, is evidence of inhibition of energy metabolism by formaldehyde.

2. The reduction of the rate of metabolic processes by formaldehyde, as demonstrated in the case of inhibition of carbohydrate metabolism, may lie at the basis of limitation of disturbances by formaldehyde, including those of hemic hypoxia.

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EFFECT OF EXCESS OF ZINC IONS ON GABA METABOLISM AND FORMATION OF THE SENSOMOTOR CORTICAL EVOKED POTENTIAL

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Zinc is a trace element with a broad spectrum of action. Its ions affect various functions of the body, but a decisive aspect of the mechanism of action of zinc is its interaction with chemical transmitters of nervous and endocrine influences, including hormones, mediators, enzymes, and so on [1, 6, 8, 12].

On the basis of histochemical and electron-microscopic data, it has now been suggested that the zinc participates in synaptic transmission, only in mossy fibers [4]. At the level of the mossy fibers of the hippocampus zinc has been shown to play an important role of maintaining long-term potentiation of excitation [5].

The state of synaptic transmission in the sensomotor cortex and of the metabolism of GABA, a meditor of inhibition [11] which plays an essential role in the central mechanism of adaptation [2], has not been studied in the presence of an excess of zinc ions and, in our view, this is an interesting topic.

In this investigation changes in the sensomotor cortical evoked potential (EP) and in concentrations of GABA, glutamic, and aspartic acids (GA and AA, respectively), and activity of the enzymes glutamate decarboxylase (GDC) and GABA transaminase (GABA-T) were studied after single and prolonged injection of various doses of zinc chloride ($ZnCl_2$).

EXPERIMENTAL METHOD

Experiments were carried out on Chinchilla rabbits weighing 2.5-2.8 kg. EP were recorded on the focus of maximal activity of the sensomotor cortex in response to electrodermal stimulation of the contralateral limb. Single stimuli 0.5 msec in duration were used for stimulation. Potentials were recorded with a D-581 dual beam cathode-ray oscilloscope (Kryžik, Czechoslovakia), after preamplification. Potentials were recorded before and after intramuscular injection of $ZnCl_2$ (single or repeated) in doses of 0.1 and 1 mg/kg body weight (calculated as the pure metal). The primary somatosensory cortical response was recorded with respect to its amplitude and temporal characteristics.

To determine amino acids, the brain was removed and treated by the method in [14] with certain modifications [13]. Free amino acids — GABA, GA, and AA, were separated by electrophoresis on paper [10]. Activity of GDC II and GABA-T was determined [7].

Concentrations of amino acids and activity of the enzymes were determined before and 30 min after intramuscular injection, single or repeated (in the course of 7, 14, and 21 days), of $ZnCl_2$ in doses of 0.1 and 1 mg/kg. The numerical data were subjected to statistical analysis [9].

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