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EFFECT OF WEAK SOLUTIONS OF ALDEHYDES ON CHANGES IN THE RAT EEG

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UDC 612.822.3.014.46:615.31:547.281

KEY WORDS: ischemia; aldehydes; EEG; CNS.

Previous investigations have shown that the safe periods of cerebral ischemia can be essentially prolonged by the use of weak solutions of aldehydes as protectors [4-6]. The protective action of aldehydes is considered to be based on inhibition of the biochemical and physiological responses. There have been many investigations of the biochemical anti-ischemic mechanisms of action of aldehydes, notably formaldehyde [2, 3, 7, 8], but little information has been obtained about physiological reactions taking place when aldehydes interact with nerve tissue. Moreover, we do not know which of these reactions may promote a favorable course of the ischemic and, in particular, the postischemic process. The aim of the present investigation was to study physiological responses of the CNS to small doses of weak solutions of aldehydes and mixtures of aldehydes.

EXPERIMENTAL METHOD

Experiments were carried out on 50 mature noninbred male rats weighing 240-280 g. Gold plated electrodes 0.4 mm in diameter were implanted into the rats' brain. The electrodes were located epidurally, bilaterally, in the medial and lateral regions of the frontoparietal cortex, according to the atlas of Paxinos and Watson [15], and were fixed by self-hardening plastics. The reference electrode was secured in the nasal bones. To apply the test solutions the right axillary artery was catheterized. Isotonic solutions of formaldehyde for glutaraldehyde, in concentrations of 0.2 and 0.02%, respectively, were injected in a dose of 0.1 or 0.2 ml/100 g body weight. A mixture of these same aldehydes in the proportion of 1:1 was used in a volume of 0.2 ml/100 g body weight. These doses of aldehydes were those which prolonged the safe period of total cerebral ischemia. As the control, the same volume of physiological saline was injected. Superficial anesthesia with hexobarbital and ether was used for the experiments. Anesthesia was induced with 1% hexobarbital solution in a dose of 0.5 ml/100 g body weight. To maintain a constant level of anesthesia, ether was inhaled. The EEG was recorded on a "San'ei" electroencephalograph (Japan). Regions of the EEG 10 sec in duration immediately before injection of the solutions and 1, 3, 5, 20, and 25 min after their injection were analyzed. In some cases, for a more detailed analysis the EEG was processed during the interval from the 5th to the 20th minute and at the 30th minute. An "Élektronika BK-0010" personal computer carried out this processing by the method of spectral analysis. The significance of differences was calculated by Cochran's test for a level of significance of $p \leq 0.05$.

EXPERIMENTAL RESULTS

Injection of physiological saline (seven experiments) caused an increase in amplitude of the EEG 20-30 sec after infusion on average by 16.3-0.7%. This change in amplitude was observed in both hemispheres in both the motor and the sensory zone of the cortex. The

Academic Group of Academician of the Academy of Medical Sciences of the USSR V. V. Kovanov, All-Union Research Center for Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Kovanov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 108, No. 10, pp. 409-412, October, 1989. Original article submitted February 12, 1989.

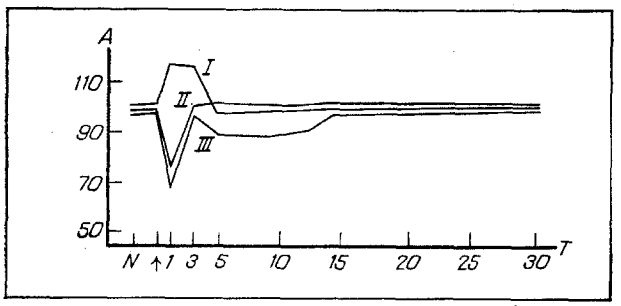

Fig. 1. Changes in power index of EEG during intra-arterial injection of formaldehyde solution. Abscissa, power index (in % of initial value); ordinate, time of experiment (in min). I) Response to injection of physiological saline; II) 0.1 ml of 0.2% formaldehyde/100 g body weight; III) 0.2 ml of 0.2% formaldehyde/100 g body weight. ↑) Time of injection of test solution.

increase in amplitude was not accompanied by any changes in the spectral composition of the EEG. The amplitude usually returned to its initial level by the 5th minute of the experiment.

When formaldehyde alone was injected (14 experiments) the spectral composition of the EEG likewise remained virtually constant throughout the period of observation. However, formaldehyde did not activate the EEG, but inhibited it. For instance, when 0.1 ml of formaldehyde/100 g body weight was injected, the amplitude of the EEG was reduced on average by 21.6 ± 1.3%. This decrease occurred 20-30 sec after infusion, but lasted for 1.5-2 min. By the end of the 3rd minute, the normal amplitude of the EEG was restored (Fig. 1).

Doubling the dose of formaldehyde enhanced the effect. At the 1st minute the amplitude was reduced on average by 29.4 ± 1.9%, significantly more than the decrease in amplitude of the EEG in response to the smaller dose. The EEG likewise returned to normal at the 3rd minute. By contrast with the previous series, inhibition of the EEG was repeated, starting on average at the 5th minute of observation, and it continued for about 8 min. In this case the decrease in amplitude was 8.2 ± 1.2%. By the 14th minute of the experiment the initial amplitude of the EEG was fully restored (Fig. 1).

The action of glutaraldehyde (11 experiments) caused a similar effect of a temporary reduction in the amplitude of the EEG, whereas its spectral composition remained virtually constant. In this case the first phase of inhibition was reduced but, on the other hand, the depth and duration of the second phase were increased (Fig. 2). An increase in the dose of glutaraldehyde led to a more marked action on the second phase of inhibition of the EEG (Fig. 2).

The action of a mixture of the two aldehydes (18 experiments) was similar in character in general with their action separately. At the 1st minute the amplitude of the EEG was profoundly inhibited on average by 42.2 ± 4.1%. The initial level was restored and the second phase of inhibition developed at the usual times (Fig. 2). This phase was characterized by considerable depth (to 62.7 ± 4.6%) and duration, which was about 18 min. The EEG was restored completely to normal after 25-27 min. In this case also, it is important to note, the spectral composition of the EEG was virtually unchanged throughout the experiment.

Early inhibition of the EEG following injection of weak solutions of aldehydes could be due to their action on vascular reflexogenic zones. Evidence in support of the reflex origin of the first phase of inhibition is given by its rapid onset and the similar times of its course in all series of experiments, although other mechanisms of "rapid" response cannot be ruled out.

We know that aldehydes become involved in metabolism very rapidly [2, 14]. Of the many reactions in which compounds of this class may take part, attention is drawn in particular to their ability to bind with monoaminergic mediators [2, 9, 10-13]. A mechanism of inhibition of the EEG linked, for example, with competitive blocking of membrane receptors by products of interaction of aldehydes and mediators may therefore be suggested. Moreover, it has been shown [1] that condensation products of aldehydes with catecholamines

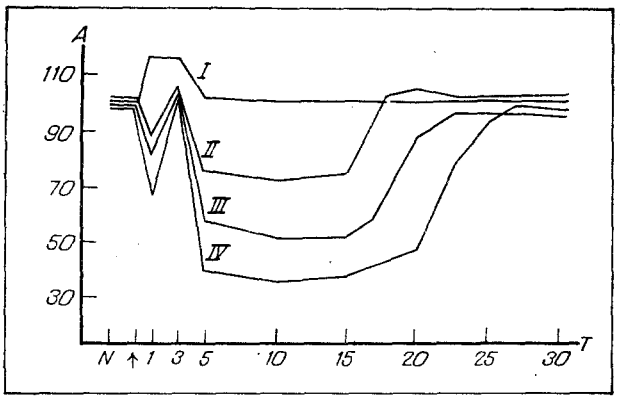

Fig. 2. Changes in power index of EEG during intra-arterial injection of glutaraldehyde solution alone and mixed with formaldehyde. I) Response to injection of physiological saline; II) 0.1 ml of 0.02% glutaraldehyde/100 g body weight; III) 0.2 ml/100 g body weight; IV) 0.2 ml of mixture of aldehydes/100 g body weight. Remainder of legend as to Fig. 1.

can potentiate the inhibitory effect of GABA and can enhance presynaptic inhibition of primary afferents. Finally, another possibility is that aldehydes simply reduce the concentration of the corresponding mediators, thereby making their action less effective. The known instability of condensation products of aldehydes with mediators can explain the reversibility of the inhibitory response of the CNS to injection of weak solutions of aldehydes. The great depth and duration of the second phase of inhibition suggests the existence of additional mechanisms. This phase is most likely connected with the action of secondary products of reactions initiated by exogenous aldehydes, but the problem of the chemical nature of these reactions and the properties of their products still remains unsolved.

The experiments revealed synergism of the action of formaldehyde and glutaraldehyde when used as a mixture. This synergism is manifested by the fact that the action of the mixture exceeded the combined action of the two aldehydes used separately.

A complex type of action of aldehydes on CNS functions was thus discovered. First, the action of aldehydes may be connected with different regulatory mechanisms, starting with receptors of reflexogenic zones and ending with participation in metabolism, which may also lead to inhibition of the electrical activity of the CNS. Second, the action of aldehydes is nonspecific, as is shown by the absence of selectivity in inhibition of EEG components. Third, the action of aldehydes in a mixture is distinctly synergic.

The view that aldehydes are highly toxic in all concentrations can be contrasted with the fact that inhibition of the EEG is fully reversible. The experimental use of weak solutions of aldehydes did not cause death of the animals during the experiment, and their behavior and neurological status in the period after the experiment were identical with those of intact animals and of control rats receiving physiological saline.

The experimental data described above explain why the most effective protection of the brain against ischemic damage occurs a short time after the end of infusion of the mixture of aldehydes. The maximal protective effect coincides in time with the development of maximal inhibition of the EEG.

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ADAPTATION TO STRESS INCREASES RESISTANCE OF THE ISOLATED HEART TO Ca^{++}-INDUCED DAMAGE BY OPTIMIZING CALCIUM PUMP OPERATION IN THE SARCOPLASMIC RETICULUM

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UDC 616.12-002:613.863[-092:612.17.014.49]-07

KEY WORDS: heart; sarcoplasmic reticulum; stress.

Adaptation to repeated stress prevents or limits disturbances of the electrical stability of the heart and arrhythmia developing in response to stress, ischemia, reperfusion, myocardial infarction, and postinfarction cardiosclerosis [2, 3, 5]. This antiarrhythmic effect is due not only to central stress-limiting mechanisms [5], for it remains largely intact in arrhythmias induced in the isolated heart by large doses of adrenalin [1], or by ischemia and reperfusion [4]. Consequently, during adaptation to stress, a sufficiently effective mechanism of limitation of arrhythmias is formed at the heart level. When this mechanism is studied, it must be recalled that as a result of the action of arrhythmogenic factors (ischemia, reperfusion, catecholamines) the inflow of Ca^{++} into the sarcoplasm is increased [6, 7].

The aim of this investigation was to assess the effect of preliminary adaptation to stress on activity of the calcium pump in the sarcoplasmic reticulum (SPR) and the resistance of the isolated heart to the arrhythmogenic and contractural effects of high Ca^{++} concentrations.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-300 g. The animals were adapted to stress, which was induced by fixing them in the supine position by their four limbs for 1 h, eight times on alternate days, with three preparatory sessions lasting 15, 30, and 45 min. The control and adapted animals were then heparinized (2000 U/kg) and anesthetized with pentobarbital (50 mg/kg), after which the heart was quickly removed and transferred into standard Krebs–Henseleit solution in a Langendorff perfusion system (11

Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 108, No. 10, pp. 412-414, October, 1989. Original article submitted February 3, 1989.

 0007-4888/89/0010-1392 $12.50