PHARMACOLOGICAL CORRECTION OF POSTVAGOTOMY HYPOXIA OF THE DIGESTIVE ORGANS BY DIBUNOL IN RATS

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Evidence has been obtained in recent years to show that a definite role in the pathogenesis of the neurodystrophic changes developing in the digestive organs after division of the vagus nerves is played by hypoxia. For instance, vagotomy has been shown to lower the partial pressure of oxygen (pO_2) in the liver, stomach, and small intestine [13]. A disturbance of the oxygen balance in organs of the digestive system under these conditions also is indicated indirectly by a change in some characteristics of mitochondria isolated from the liver of vagotomized rats, which are of the hypoxic type [7]. At the same time, we know that hypoxia is a sufficiently powerful factor to induce lipid peroxidation (LPO), more especially in mitochondrial membranes [4, 5]. An indication of the possibility of nonphysiological intensification of free-radical oxidation of lipids in the digestive organs following a disturbance of their vagal innervation is given by the results of investigations [9, 10] which demonstrated changes characteristic of the state of LPO activation in the activity of certain enzymes (superoxide dismutase, xanthine oxidase) and an increase in the concentration of malonic dialdehyde (an end product of LPO) in the liver Intensification of LPO, leading to disturbance of the molecular organization of the membranes, their permeability and microviscosity, and also the functioning of membrane-bound enzymes and receptors, may in turn aggravate the aftereffects of hypoxia [11].

On the basis of these considerations an attempt was made at pharmacological correction of the hypoxic state developing in the digestive organs of rats after vagotomy, by means of a synthetic antiradical antioxidant belonging to the group of spatially screened phenols, namely dibunol (ionol).

EXPERIMENTAL METHOD

Experiments were carried out on 90 male albino rats weighing 180-210 g, on 36 of which bilateral subdiaphragmatic vagotomy was performed. In the experiments of series I, intact (undergoing a mock operation after 24 h) and vagotomized rats were tested 1, 7, 14, 30, and 60 days after the operation, without any additional procedure. In series II, starting with the 2nd day after the operation, and on alternate days, the vagotomized rats received intraperitoneal injections of dibunol (2, 4, 6-di-tert-butyl-4-methylphenol) in a dose of 25 mg/kg (the dose was recommended by the Sector of Kinetics of Biological Processes, Research Institute of Chemical Physics, Academy of Sciences of the USSR) in a 3% solution of Tween-80 for 29 days, and these rats were investigated 30 days after the operation. This time was chosen on the basis of the results of the experiments of series I, according to which the most marked changes in the oxygen balance were observed during this period (Table 1). Vagotomized rats not receiving dibunol served as the control. In series III dibunol or solubilized

*Deceased.

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TABLE 1. Partial Pressure of Oxygen (pO_2 in mm Hg) in Digestive Organs of Rats Undergoing Vagotomy and Receiving Dibunol (M ± m)

Experimental conditions	Liver	Stomach	Small intestine
Intact (INT)	27,3±2,8	76,9±3,7	62,6±5,9
INT + dibunol	24,9±2,2	80,0±4,6	67,1±3,8
INT + Tween-80	25,5±3,0	79,0±3,9	60,5±4,0
Laparotomy	12,0±2,8*	43,0±3,4*	41,6±2,0*
1 Day after vagotomy	11,7±0,4*	45,6±5,0*	35,6±1,5*
7 Days after vagotomy	20,6±2,6	62,5±4,9	37,4±2,2*
7 Days after vagotomy	14,7±3,0*	60,8±6,0	62,0±3,4
7 Days after vagotomy	12,8±2,9*	46,4±5,3	34,5±3,5*
30 Days after vagotomy + dibunol	26,2±4,9**	70,8±5,8**	61,5±5,2**
7 Days after vagotomy	16,2±1,2	40,8±6,8*	49,2±1,1

Legend. *$p < 0.05$ compared with INT, **$p < 0.05$ indicates statistically significant differences between vagotomized rats receiving and not receiving dibunol.

Tween-80 in the same doses was injected into intact animals during the same period pO_2 was measured in the liver and muscular coat of the fundus of the stomach and the proximal part of the jejunum in rats anesthetized with urethane (150 mg/100 g) by a polarographic method [1], using a platinum indicator electrode and a calomel reference electrode. Recordings of pO_2 were made at 3-5 points within the region of the organs to be tested. The results of the measurements were subjected to statistical analysis by the method in [12].

EXPERIMENTAL RESULTS

The results (Table 1) show that pO_2 in the liver of the intact rats was 27.3 ± 2.8, in the stomach 76.9 ± 3.7, and in the small intestine 62.6 ± 5.9 mm Hg. A fall of pO_2 was observed 24 h after vagotomy in all the organs tested; similar changes took place also in rats undergoing the mock operation. After 7 days a decrease was found in pO_2 in the small intestine, after 14 days in the liver, and after 30 days in all the organs studied (on the borderline of significance in the stomach). A fall of pO_2 was found only in the stomach 60 days after the operation. Injection of dibunol into vagotomized rats for 29 days (starting with the 2nd day after the operation) led to an increase in pO_2 in all the organs studied up to a level commensurate with that in the intact animals. The control experiments showed that neither dibunol nor the solubilizing agent Tween-80 had any significant effect on this parameter in intact rats.

To sum up these results it can be concluded that division of the vagus nerves leads to the development of a state of hypoxia in the diges.tive organs (liver, stomach, small intestine), which is most marked after 30 days. The leading pathogenetic factor lying at the basis of this state is probably a vascular factor, for it has been shown that vagotomy is accompanied by reduction in the rate of the regional blood flow [14], disturbance of the microcirculation [6], and disturbance of capillary permeability [8] in organs of the digestive system. The fall of pO_2 in an organ (tissue) leads regularly, as we know, to activation of LPO [2, 4]. Meanwhile, under conditions of vagotomy, relative predominance of tone of the sympathetic nervous system may serve as the factor inducing (or intensifying) LPO, for we know that adrenalin and noradrenalin activate this process [16]. It must be recalled that these two mechanisms may also act synergically, for it has been shown that oxygen deficiency increases the sensitivity of cells to the LPO-activating effect of catecholamines [17]. A nonphysiological intensification of LPO may involve the smooth muscle cells of intramural blood vessels, causing their spasm and consequent worsening of the blood supply to the organ [15]. A vicious circle arises: hypoxia leads to activation of LPO, and the raised level of LPO maintains and aggravates the hypoxia. Facts and arguments given above suggest that the favorable effect of dibunol on oxygen metabolism in the digestive organs after vagotomy, demonstrated in this investigation, is mainly due to lowering of the LPO level in the smooth muscle cells of their blood vessels, normalization of vascular tone, and improvement of the blood supply. Moreover dibunol, like other antioxidants, which intensify the coupling of oxidation and phosphorylation in the mitochondria and thus prevent exhaustion of the ATP reserves, reduces the oxygen consumption of the cells and may contribute to the raised pO_2 level in the organs [3].

It can be concluded from the results of this investigation that the synthetic phenolic antioxidant dibunol has a normalizing action on hypoxia developing in organs of the digestive system (the liver, stomach, and small intestine) arising after vagotomy.

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