The Correction of Postvagotomy Disturbances of Small Intestine Motility with Antihypoxants and Antioxidants

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Hypoxia and activation of lipid peroxidation (LPO) are well known as pathogenic factors in the development of neurodystrophy of the digestive system as a result of damage to the parasympathetic innervation. It has been shown that vagotomy results in a decrease of the oxygen tension in the liver, stomach, and small intestine [7] and causes biochemical changes specific for the state of nonphysiological LPO onset (a rise in the level of malonic dialdehyde and superoxide dismutase activity, a decrease in xanthine oxidase activity, and so on) [3,4]. A definite correlation has been established between the depth of hypoxia and LPO activation, on the one hand, and the degree of manifestation of morphofunctional reorganization, on the other [8,12]. However, a number of important aspects in the pathogenesis of the postvagotomy syndrome and, in particular, the role of these factors in the development of disorders in small intestine motility remain unclear. At the same time, clinical findings attest to a leading role of intestinal complications in vagotomized patients undergoing surgery for duodenal ulcer [2].

The present investigation was performed to study the effects of pharmacological correction of small intestine motility disturbances resulting from vagotomy, using the antihypoxant sodium γ-hydroxybutyrate and the antioxidant dibunol.

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MATERIALS AND METHODS

Experiments were carried out on 104 male albino rats weighing 180-350 g (58 animals were subjected to complete bilateral subdiaphragmatic vagotomy). In the first experimental series the intact (sham-operated 1 day later) and the vagotomized rats were examined 1,3,7,14,30,60, and 220 days after the operation without any additional treatment. In the second series, from the first to the 30th day after the operation the vagotomized animals were injected i.m. with sodium γ-hydroxybutyrate in a dose of 300 mg/kg twice daily . In the third series the vagotomized rats were injected i.p. with dibunol (2,6-ditert-butyl-4-methylphenol) in a dose of 25 mg/kg/day on 3% Tween-80 from the second day postoperation for 29 days. Vagotomized animals without drug administration were used as controls. In the fourth series sodium γ-hydroxybutyrate and dibunol were administered to intact animals according to the same scheme. The rats of experimental II-IV groups were examined 30 days after vagotomy. The animals fasted 16-18 h prior to experimentation. Intestinal motility was assessed by the electrical activity of the smooth muscles, registered in acute experiments under urethane anesthesia (1.5 g/kg). Bipolar silver electrodes of the softened clip type were fixed in the proximal portion of the small intestine (jejunal part), and electromyographic tracings were performed according to the bipolar scheme of a Mingograf-82 polyphysiograph at a sensitivity level of 0.2 mV, a time constant of 1 sec and an upper frequency limit of

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TABLE 1. Changes in Indexes of Electromyographic Tracings of Jejunal Smooth Muscles at Different Times Post-Vagotomy

Indexes	Intact	Sham-operated	Time, days						
			1	3	7	14	30	60	220
I	32.3±0.98	28.2±2.89	30.2±0.50	26.1±0.92*	31.9±0.75	24.8±2.4	32.8±1.03	28.3±1.11	32.0±1.20
II	2.44±0.21	3.16±0.41	3.93±0.49	1.92±0.15	2.76±0.06	2.47±0.24	3.58±0.21*	2.58±0.42	2.36±0.30
III	0.076±0.008	0.111±0.008	0.130±0.011	0.078±0.008	0.086±0.002	0.105±0.016	0.109±0.004*	0.093±0.01	0.074±0.01
IV	2.26±0.14	1.67±0.06*	1.70±0.03*	1.82±0.04*	1.88±0.03	1.87±0.08	1.74±0.03*	1.68±0.06*	2.40±0.02
V	6.09±0.35	5.52±0.86	4.67±0.53	7.21±0.61	7.35±0.78	7.37±0.78	6.22±0.14	6.80±1.02	6.36±0.35
VI	0.36±0.02	0.31±0.04	0.37±0.04	0.25±0.03*	0.24±0.02*	0.26±0.02*	0.28±0.01*	0.28±0.04	0.37±0.02
VII	2.38±0.10	2.57±0.17	2.62±0.33	2.31±0.28	1.89±0.22	2.34±0.15	2.40±0.18	0.1.78±0.23	2.30±0.19

Note. Here and in Table 2 : I) frequency of slow electrical waves (SEW); II) frequency of SEW groups; III) ratio of frequency of SEW groups to frequency of SEW proper; IV) ratio between maximal and minimal amplitudes in an SEW group; V) number of SEW in a group; VI) steepness of changes of SEW amplitude in a group (estimated as the quotient of VI/V); VII) ratio of duration of SEW groups to intervals between them; asterisk means reliable differences ($p<0.05$); one asterisk for the differences between vagotomized and control rats; two asterisks for the same between drug-treated and untreated vagotomized rats.

70 Hz. The tracings were subjected to multifactor quantitative analysis as described previously [10]. The data were processed statistically using Strelkov tables [5].

RESULTS

The findings demonstrated (Table 1) that vagotomy in intact rats is accompanied by specific changes in the electrical activity of the small intestine , which in the early stage (1-7 days) manifests itself in the following: an increase in the ratio of the frequency of the groups of slow electrical waves (SEW) to the SEW frequency proper (day 1), while the frequency of SEW decreases (day 3), an increase of the ratio between the maximal and the minimal amplitudes of SEW in its groups (days 1-3) and a decrease in the steepness of the amplitude changes in the SEW groups (days 3 and 7). In a later period (days 14-220) the changes in the amplitude of SEW become less steep in the SEW groups (days 14 and 30), thus diminishing the ratio of the maximal SEW amplitude to the minimal amplitude in the SEW groups (days 30 and 60), and the frequencies of both the SEW groups and their ratio to the SEW proper increase (day 30). Multifactor analysis of the above-described electrical activity of the bowel, carried out by plotting the respective nomograms, revealed pronounced disturbances of function 30 days after the vagotomy procedure. Administration of sodium γ-hydroxybutyrate to the vagotomized rats resulted in a nearly total correction of the denervation-induced impairment of the bowel electrical activity: three out of the four indexes of electromyographic evaluation, that significantly differed from the control values under conditions of vagotomy, were restored to the initial values . The parameters returning to the control values under the action of sodium γ-hydroxybutyrate were the ratio between the frequencies of SEW groups and the SEW proper, the ratio of the maximal and the minimal amplitudes of the potentials in the SEW groups, and the steepness of amplitude variations in a SEW group. The favorable effect of dibunol was less pronounced, achieving the normalization of just two indexes: the ratio of frequencies of SEW groups to the SEW and the steepness of the amplitude changes in the groups (Table 2). The control experiments revealed that the drugs did not affect bowel motility in any reliable way.

These findings suggest that severing the vagus nerves results in a complex of specific changes in intestinal electrical activity, which is defined in the attenuation and distortion (dyskinesia) of the motility of the organ under these conditions. This phenomenon is probably related to a circulatory hypoxia, as is confirmed by the decrease in the

TABLE 2. Changes in Electromyographic Indexes of Jejunal Smooth Musculature under Conditions of Vagotomy and Administration of Sodium γ-Hydroxybutyrate and Dibunol.

Index	Intact animals	Vagotomy, 30 days	Vagotomy+GHBA-Na	Vagotomy+Dibunol
I	32.8±0.1	32.8±1.03	33.6±0.09	34.9±1.19
II	2.44±0.21	3.58±0.21*	2.78±0.07	3.01±0.17
III	0.076±0.008	0.109±0.004*	0.083±0.005**	0.086±0.006**
IV	2.26±014	1.74±0.03*	2.19±0.04**	1.96±0.06
V	6.09±0.35	6.22±0.14	5.60±0.21	4.90±0.14
VI	0.36±0.02	0.28±0.004*	0.39±0.01**	0.40±0.03**
VII	2.38±0.10	2.40±0.18	2.43±0.15	1.79±0.19

oxygen tension in the muscular layers of the intestine, which in turn may be correlated with the decrease in the rate of regional circulation demonstrated on the same experimental model [8]. It may be concluded that LPO activation, together with hypoxia, play a specific role in the pathogenesis of intestinal motility disturbances in cases of vagotomy. This is supported by such facts as the increase in the reduction potential of the bowel homogenate (the capacity to reduce Fe^{3+} to Fe^{2+}) and the elevated catalytic activity of intestinal catalase in the vagotomized rats [9]. If the LPO activation affects the smooth myocytes of the intraorganic vessels, then it may cause vasoconstriction and thereby maintain and exacerbate hypoxia [11]. From the above findings and considerations we can assume that the favorable effects of sodium γ-hydroxybutyrate and dibunol on the state of the contractile apparatus of the murine small intestine under vagotomy may be related to the following. It is known that γ-hydroxybutyric acid and its salts, upon entering the cell via a Robertson shunt, are converted to succinate , which is drawn into the tricarbonic acid cycle, which increases the efficiency of the cell respiration inhibited by hypoxia [6]. Dibunol, as a strong anti-free radical agent. decreases the LPO level in the smooth myocytes of vessels, normalizes their tonus, and thereby improves the blood supply to the organ. In addition, dibunol, like to other antioxidants, conjugates the oxidation process with phosphorylation in the mitochondria and prevents ATP depletion, decreases the oxygen consumption by cells [1], and may restore the oxygen tension in the intestine.

Thus: 1) vagotomy is followed by changes in the intestinal electrical activity that attest to a weakening and distortion of the motor function of the organ, whereby the changes are most pronounced in the period 30 days post-vagotomy; 2) sodium γ-hydroxybutyrate and dibunol (to a lesser degree) normalize the vagotomy-impaired functional state of the intestinal contractile apparatus.

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