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Review Article

Reactivity of Organs Under Conditions of Denervation Syndrome

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Summary

The study: Of the reactive properties of organs with impaired innervation has a long history, but the question of the state of reactivity of organs (tissues) located outside the denervation region remains poorly understood.

Materials and methods: In the experiment, 26 white male rats weighing 180–210 g were used. Initially, intact and vagotomized (14 days after the operation) animals were subcutaneously injected with carbon tetrachloride (at a dose of 3.2 g/kg in the form of a 50% oil solution) and removed from the experiment 24 hours after inoculation. The state of the erythroid germ of hematopoiesis was assessed based on the analysis of the morphological and functional characteristics of peripheral blood erythrocytes (ER): diameter, area, integral (indicator reflecting the amount of hemoglobin in the ER) and specific (indicator reflecting the concentration of hemoglobin in the ER)). optical density, polarization, factor percentage of deformed Er and Er with anomalous distribution of optical density, shape of Er, anisocytosis, anisochromia, etc.

Results and its discussion: It has been shown that intoxication of ChCA in initially intact rats is accompanied by an increase in the value of the Er form factor, the content of deformed Er and Er with an abnormal distribution of optical density, as well as a tendency to increase their polarization value. When transection of the vagus nerves, there is an increase in the area of Er and a tendency to an increase in the values of polarization, anisochromia, and the content of deformed Er and Er with an abnormal distribution of optical density. Under conditions of ChChU intoxication in vagotomized rats, an increase in the content of Er with an abnormal distribution of optical density, as well as a decrease in the value of anisochromia, was revealed. In addition, a trend towards an increase in the content of deformed Er and a decrease in the value of anisocytosis was found.

Conclusions: Based on the data obtained, it is possible to conclude that there is a change in the reactivity of organs (in particular, the red bone marrow and spleen) located outside the denervated area, which is the basis for the idea of a neurodystrophic process as a systemic response of the body to a violation of its innervation relations. structural components.

Keywords: Denervation syndrome; Erythrocytes; Liver; Neurodystrophic process

The study of the reactive properties of organs with impaired innervation has a long history, but the question of the state of the reactivity of organs (tissues) located outside the region of denervation remains little studied. Obviously, the development of this aspect of the doctrine of the neurodystrophic process is important for the formation of a holistic picture of this phenomenon. In the present work, an attempt was made to study the reactive properties of the blood system (in particular, the erythroid germ of myelopoiesis) under conditions of denervation syndrome caused by a violation of the integrity of the nerve conductors. An experimental model was acute Carbon Tetrachloride Poisoning (CCT) against the background of bilateral transection of the vagus nerves in rats. The choice of CTC as an irritant factor is due, on the one hand, to the fact that its biological effects and their molecular mechanisms are well studied [1], on the other hand, due to the rather wide distribution of this toxicant in the environment (it is used in various areas of the national economy and veterinary medicine) [2]. In addition, CHU is used in experimental practice to simulate acute and chronic hepatitis, various forms of toxic conditions [3]. We chose vagotomy as a method of denervation, based on the purpose of this study and the main requirement of the model - the creation of a fairly large region of denervation (in rats, the area of distribution of the vagus nerves under the diaphragm covers the stomach, the entire small intestine, liver, pancreas, not affecting the bone apparatus and, accordingly, the red bone marrow.This also took into account the fact that organ-preserving operations used to treat duodenal ulcer and stomach ulcers are often associated with the intersection of the vagus nerves or their branches [4,5].

Materials and Methods

In the experiment, 26 white male rats weighing 180–210 g were used. Initially intact and vagotomized (14 days after the operation) animals were injected subcutaneously with CCA (at a dose of 3.2 g/kg in the form of a 50% oil solution) and removed from the experiment through 24 hours after inoculation. Intact and vagotomized rats not subjected to intoxication served as controls. The assessment of the state of the erythroid germ of hematopoiesis was carried out on the basis of the analysis of the morphological and functional characteristics of Erythrocytes (ER) of peripheral blood. To do this, on unstained blood smears fixed in formaldehyde vapor, using computer morphodensitometry (on the complex of automated microscopy MEKOS-Ts2), the following Er parameters were determined: diameter, area, integral (indicator reflecting the amount of hemoglobin in Er) and specific (indicator reflecting the concentration of hemoglobin in Er) optical density, polarization, shape factor Er, anisocytosis, anisochromia, the percentage of deformed Er and Er with an abnormal distribution of optical density. To assess the structural and functional status of the liver, morphological (specific area of necrosis zones and sinusoidal capillaries), sinusoid shape factor and area of the nucleus of hepatocytes and biophysical (total water content and spin-lattice - T1 and spin-spin - T2 relaxation times) were used.) characteristics, systems of serum albumins (SA) - biochemical (total albumin concentration in serum) and biophysical (binding constant, number of binding sites per molecule, quenching constant of the fluorescent probe associated with SA 1-(Phenylamino)-8-sulfonaphthalene (ANS) with potassium nitrate Kt, the proportion of fluorescence bound ANS available for the quencher - E) parameters.

The significance of differences between the experimental and control data was assessed using Student's t-test. Statistical data processing was carried out using the program "Statistika 12.0". The results are presented as the arithmetic mean and the standard error of the mean.

Results and Discussion

It was shown (Table 1) that CCA intoxication in initially intact rats is accompanied by an increase in the value of the form factor Er, the content of deformed Er and Er with an abnormal distribution of optical density, as well as a tendency to an increase in the value of their polarization. When transection of the vagus nerves, there is an increase in the area of Er and a tendency to an increase in the values of polarization, anisochromia, and the content of deformed Er and Er with an abnormal distribution of optical density. Under conditions of ChChU intoxication, vagotomized rats showed an increase in the content of Er with an abnormal distribution of optical density, as well as a decrease in the value of anisochromia. In addition, a trend towards an increase in the content of deformed Er and a decrease in the value of anisocytosis was found. It should be noted that in animals of this group, along with destructive-dystrophic changes in ER, signs of compensatory-adaptive rearrangements were found, in particular, an increase in the integral optical density of ER, which reflects, as mentioned above, the amount of hemoglobin in them.

Options / Series		Average diameter (µm)	Square (µm²)	Polarization	Shape Factor	Integrated optical density	Specific optical density	Anisocinosis	Anisochromia	Deformed erythrocytes	Erythrocytes with abnormal optical density distribution	Complex integral indicator
Intact	Control	6.54÷6.77	33.73±36.11	0.04±0.03	14.21±14.92	10.39±8.74	0.31± 0.24	5±5	14±17	0.56±0.35	2.78±2.09	
		5.50÷6.39	23.87±32.17	0.06±0.04	14.38±14.14	7.83±8.75	0.33±0.27	8±5	16±16	0.34±0.45	0.68±0.90	
		6.64÷6.63	34.73±34.62	0.03±0.07	14.16±14.35	10.22±12.61	0.29±0.36	5±5	13±14	0±2.26	1.54±2.26	0
		6.41÷0.46	32.54±4.44	0.045±0.016	14.36±0.28	9.76±1.70	0.30±0.04	5.50±1.23	15.00±1.55	0.43±0.10	1.71±0.82	
	carbon tetrachloride intoxication	6.82÷6.42	36.68±32.48	0.03±0.05	14.20±14.24	12.16±1.42	0.33±0.35	6±6	15±16	2.51±7.36	6.46±7.67	
		6.32÷6.50	31.42±33.33	0.05±0.04	14.15±14.42	10.32±10.13	0.33±0.30	5±6	17±17	0±1.68	6.40±6.00	
		6.48	33.07	0.05	14.39	8.29	0.25	6	21	3.78	1.9	1.15
		6.51÷0.19	33.40±1.98	0.044±0.009	14.28±0.12**	11.00±0.96	0.31±0.04	5.80±0.45	17.40±1.28**	3.83±2.51**	5.69±2.21**	
		(+1.6%)	(+2.6%)	(-2.2%)	(-0.5%)	(+12.7%)	(+3.3%)	(+5.5%)	(+16.0%)	(+790.7%)	(+232.8%)	
Vagotomy	Control	6.67÷6.50	34.98 ±33.31	0.03±0.06	14.25±14.76	10.47±8.73	0.30±0.26	5±6	16±16	0.93±8.73	1.55±4.01	
		6.41÷6.59	32.33± 34.20	0.05±0.06	14.87±15.09	10.34±10.55	0.32± 0.31	5±6	16±15	3.32±3.07	1.72±0	
		6.61	34.45	0.06	14.85	11.09	0.32	6	14	1.04	1.56	0 (3.86)
		6.56÷0.10	33.85±1.04	0.052±0.013	14.76±0.30*	10.24±0.88	0.30±0.03	5.60±0.55	15.40±0.89	2.09±1.28*	1.61±0.09	
	carbon tetrachloride intoxication	6.65÷6.75	34.82±35.83	0.04±0.04	14.57±14.68	9.93±9.68	0.29±0.27	5±6	15±15	4.58±1.83	11.26±3.91	
		6.74÷6.50	35.74±33.31	0.04±0.04	14.33±14.54	10.87±10.52	0.30±0.32	5±6	16±17	2.93±3.89	8.94±7.39	
		6.67÷6.51	35.02±33.35	0.05±0.04	14.27±13.95	10.19±11.41	0.29±0.34	5±5	15±15	4.02±1.08	9.49±1.95	3.65
		6.64÷0.11	34.68÷1.12	0.042±0.004	14.39±0.27**	10.43±0.64	0.30±0.02	5.33±0.52	15.50±0.84	3.06±1.36	7.43±2.51**	
		(+1.2%)	(+2.5%)	(-19.8%)	(-2.5%)	(+1.9%)	0%	(-1.3%)	(+0.6%)	(+46.4%)	(+361.5%)	

Table 1: Changes in the morphological parameters of erythrocytes in initially intact and vagotomized rats under conditions of carbon tetrachloride intoxication (24 hours).

Series	Options	Sinusoid area (µm²)	Perimeter of the sinusoid (µm)	Sinusoid shape factor	Cytoplasmic area (µm²)	Core area (µm²)	Hepatocyte area (µm²)	Nuclear-plasma relation	liver immunocyte cells
Intact	No seed	32.3 ± 0.8	33.1 ± 1.5	37.5 ± 2.1	173.4 ± 3.2	40.7 ± 1.2	214.2 ± 4.4	0.19±0.004	0
	carbon tetrachloride intoxication	43.4 ± 2.8**	37.9 ± 1.7(*)	34.1 ± 1.2	181.6 ± 5.4	45.8 ± 1.1**	227.5 ± 13.3	0.21 ± 0.01	0.42
Vagotomy	No seed	46.5 ± 3.3*	30.1 ± 2.8	42.1 ± 1.2	144.8± 2.4*	41.3 ± 1.8	186.1 ± 12.2	0.23 ± 0.02	0
	carbon tetrachloride intoxication	78.2 ± 4.7**	34.2 ± 2.7	30.8 ± 1.3**	162.8 ± 6.9	44.0 ± 2.6	206.8 ± 7.9	0.21±0.005	0.77

Table 2: Changes in the morphological parameters of the liver of initially intact and vagotomized rats in case of tetrachloromethane poisoning (24 hours).

As shown by microscopic examination of the liver (Table 2), within 24 hours after the introduction of ChCA, foci of centrilobular necrosis appear in the organ. In areas of necrosis, infiltration with lymphoid-histiocytic elements is often noted. Some hepatocytes (as a rule, adjacent to the areas of necrosis) are distinguished by vacuolized cytoplasm, a compacted or sharply clarified nucleus (altered hepatocytes). Along with this, there is an expansion of intralobular sinusoidal capillaries and blood stasis in them. Morphometric analysis showed that the specific area occupied by necrotic hepatocytes is 11.2 + 1.0%, altered parenchymal cells - 40.5 + 4.3%, intact hepatocytes - 48.3 + 5.0%, sinusoidal capillaries - 11.9 + 0.1%. With CTC seeding, the area of sinusoids increases by 34.9% ($p < 0.05$), the area of the nucleus increases by 12.5% ($p < 0.05$). During vagotomy, the area of sinusoids in animals with CCM additionally increases by 68.1% ($p < 0.05$), the shape factor of sinusoids and the area of the nucleus increase by 6% ($p < 0.05$). Under these conditions, biophysical analysis revealed a significant increase in the total water content in the liver, an increase in T_1 and T_2, and a decrease in the T_1 / T_2 ratio.

The fact that, in this case, the SA binding reserve, calculated as the ratio of the average number of binding sites on one protein molecule to the total concentration of albumin in serum, increases, in all likelihood, indicates that under conditions of CTC intoxication, a partial renewal of the population of molecules occurs. SA due to the mobilization of their intracellular reserves or (and) enhanced de novo synthesis (compensatory reaction). Of particular note is the fact of a more than threefold increase in the quantum yield of ANS in combination with SA in animals exposed to CTC. The phenomenon, apparently, is based on a change in the nature of the interaction between SA and ANS under these conditions - SA molecules not modified under the action of a toxicant and mobilized from reserves "swallow" the probe more deeply and thus effectively shield it from water molecules. At the same time, this circumstance does not mean at all that the probe in the structure of the complex becomes less accessible to certain quenchers.An analysis of the ANS fluorescence quenching curves in the "SA-ANS" complex demonstrated an increase in the accessibility of the probe to such a quencher as potassium nitrate, as evidenced by an increase in D and a decrease in Kt. Conformational transformations of the SA molecule, leading to a change in the type of its interaction with ANS, are presumably due to a decrease in the number of amino groups (and, accordingly, an increase in the negative charge) on the protein surface as a result of their "neutralization" by aldehydes, products of lipid peroxidation, which is known to be activated under given conditions.

As a result of the study of the SA system, it was found that CHU intoxication is accompanied by a clear tendency to a decrease in the total concentration of SA in the blood (by 13.8%), the cause of which, most likely, is a decrease in the level of its synthesis due to the destruction of hepatocytes or (and) increased elimination of defective protein molecules from the bloodstream. At the same time, the total concentration of binding sites in serum does not change significantly, since their average number per protein molecule increases. Under these conditions, the binding constant changes (decreases) more significantly, which leads to a noticeable decrease in the average binding capacity of the serum.

Summarizing and analyzing the obtained data, we can state the presence of some similar changes in the rearrangement of the ER morphology in initially intact and vagotomized rats in case of poisoning with ChCA, in particular, an increase in the content of ER with an abnormal distribution of optical density and deformed ER (the last change is at the level statistical trend in vagotomized animals). Taking into account the results of studies performed on similar experimental models by other authors [6], it can be assumed that these changes are due to the direct influence of CCA and its biotransformation products (trichloromethyl free radical, chloroform, hexachloroethane, carbonyl chloride, etc.).) on the blood Er, red bone marrow and the organs of elimination of the Er, primarily the spleen. At the same time, characterizing the response of erythron to CTC intoxication under conditions of vagotomy in general, it should be noted that it has a distinct specificity. Thus, the changes in ER morphology described above, common for both series of rats, in vagotomized animals are expressed to a much lesser extent: the content of deformed ER increases by 45.2% (against 416.7% in initially intact), the content of ER with an abnormal distribution optical density increases by 73.9% (against 144.7%). In contrast to the initially intact rats, vagotomized rats show an increase in the integral optical density Er, and a decrease in the values of anisocytosis and anisochromia. The peculiarities of the morphological rearrangements of Er under conditions of CTC intoxication between initially intact rats and rats that underwent vagotomy are most likely due to the fact that the response of erythron to the administration of a toxicant in the latter group of animals is realized against a different background. As mentioned above, vagotomy has a certain effect on erythropoiesis, which manifests itself in an increase in the area of Er and a tendency to increase the values of polarization, anisochromia, and the content of deformed Er and Er with an abnormal distribution of optical density. It can be assumed that these changes are due to the following factors. Thus, pathological impulses from the central ends of cut vagus nerves, causing irritation of the corresponding nuclei of the hypothalamus, can disrupt the functioning of nerve centers located in the same area of the brain that regulate hematopoiesis.

The validity of this assumption is indirectly confirmed by the results of studies in which local stimulation of various nuclear structures of the hypothalamus was carried out, which caused regular rearrangements of the red blood state. In addition, it should be taken into account that in the organs located in the focus of denervation, the number of mast cells significantly increases, which, as is known, actively produce cytokines (interleukin-1, gamma-interferon, tumor necrosis factor), which receive direct participation in the regulation of erythropoiesis [7]. Once in the general circulation and reaching the red bone marrow, these humoral agents can have a certain effect on the process

of hematopoiesis. Along with this, a certain contribution to the development of the studied pathological condition can be made by the "gastric" factor. Thus, it has been shown that vagotomy is accompanied by significant structural and functional changes in the parietal cells of the gastric glands [8], which produce hydrochloric acid components and produce the internal factor of Castle (hydrochloric acid is necessary for the effective absorption of iron, the factor of Castle - vitamin B12). In addition, vagotomy, as a rule, is accompanied by the development of gastrostasis (prolonged stagnation of dense food masses in the stomach), including in rats [9]. At the same time, it has been established that irritation of the gastric mechanoreceptors leads to pronounced quantitative and qualitative changes in red blood parameters.

Conclusions

On the basis of the data obtained, it is possible to conclude that there is a change in the reactivity of organs (in particular, those responsible for the production of ER - red bone marrow and spleen) that are outside the denervated area, which is a strong argument in favor of the concept of neurodystrophic process as a systemic response. reactions of the body to the violation of the innervation relations of its structural components.

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