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Morphofunctional changes in the animal organisms under oral exposure to anatoxin-a in subchronic experimental settings

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ABSTRACT

Introduction. Anatoxin-a (2-acetyl-9-azabicyclo[4.2.1]non-2-ene) produced by blue-green algae of the genera *Dolichospermum* (*Anabaena*), *Aphanizomenon*, *Cylindrospermum*, *Oscillatoria*, *Planktothrix* and *Raphidiopsis*, which are widely spread in the reservoir waters, including those serving as drinking water supply sources for the population. At the same time, the lack of information on the toxic effect of low doses of anatoxin-a (ATX-a) on the morphofunctional condition of warm-blooded animals' internal organs under prolonged oral intake into the body remains poorly researched.

The aim of the research was to study morphofunctional changes in internal organs under the influence of anatoxin-a on the white rat bodies at intragastric intake in subchronic pilot experiments.

Material and methods. ATX-a as a certified reference sample in 1% acetic acid solution was dosed daily to male white rats in doses of 0.01; 0.1 and 1.0 µg/kg for 90 days. Morphofunctional changes in 13 internal organs were assessed: thyroid gland, thymus, heart, lung, stomach, liver, spleen, pancreas, ileum, colon, kidney, adrenal glands, testes.

Results. It was established that administration of ATX-a in the animals' body at a dose of 1.0 µg/kg b.w. was followed by significant changes in the same organs compared to the control: testes (2.7-fold increase in the number of spermatogenic cells in some seminal tubules), thymus (4-fold increase in the proportion of lipomatous areas), stomach (3.5-fold increase in hypersecretion of intrinsic glands, 4-fold – disturbance of borders between mucosa and submucosa, 2.7 times – thinning of connective tissue fibres), colon (hypersecretion and 2.4 times increase of blood vessels), pancreas (2.3 times increase of Langerhans islets fibrosis). When exposed to ATX-a at doses of 0.1 and 1.0 µg/kg b.w. in the adrenal glands, an increase in ectopy by 3.3 and 2.5 times, respectively, compared to the control was observed.

Limitations. The study is limited by the intragastric intake conditions and the use of one species and sex of warm-blooded animals in the experiment.

Conclusion. Morphofunctional changes were revealed in the testes, thymus, stomach, colon, pancreas, adrenal glands of white rats under oral exposure to ATX-a in a subchronic experiment.

Keywords: *anatoxin-a; subchronic experiment; intragastric intake; internal organ morphofunctional changes, general toxic effect*

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Introduction

Anatoxin-a (ATX-a) is a low molecular weight bicyclic alkaloid with a molecular weight of 165.237 g/mol and a boiling point of 291 °C [1]. The empirical formula of ATX-a is $C_{10}H_{15}NO$, CAS 64285-06-09.

ATX-a was first isolated from cyanobacteria (CB) of the species *Dolichospermum* (*Anabaena*) *flos-aquae*, and later its production was established by other CB species of the genera *Aphanizomenon*, *Cylindrospermum*, *Oscillatoria*, *Planktothrix* and *Raphidiopsis* [2, 3].

The main impact of ATX-a on humans occurs when drinking water is consumed if surface reservoirs are used as a source of water supply. Other routes of entry are of less importance – inhalation of water aerosols during showering, consumption of food contaminated with cyanotoxin, use of algae-based food additives [4–8].

In a number of foreign researches, acute toxicity has been studied and the values of average lethal doses (LD_{50}) of ATX-a have been established for various routes of entry into the body of animals. Stevens D.K., Krieger R.I. in experiments on male Swiss Webster ND-4 mongrel mice with intraperitoneal administration established an LD_{50} equal to 0.21 mg/kg of body weight, under the conditions of the oral route of entry, the LD_{50} value was 13.3 mg/kg of body weight [9]. In studies of Puddick et al. on female Swiss albino mice with oral administration of ATX-a, the LD_{50} value was established at the level from 8 mg/kg to 25 mg/kg of body weight [10]. The review article by Testai E. et al presents the results of a number of experimental studies, which indicate that the acute toxicity of ATX-a in mice with intraperitoneal intake (LD_{50}) is 0.25 mg/kg body weight [11].

In our previous studies, it was found that the general toxic effect of ATX-a at a dose of 1.0 mcg/kg of body weight was manifested by a significant decrease in the number of leukocytes, lymphocytes and monocytes, a significant increase in serum total protein, cholesterol and a decrease in triglycerides compared with the control group of animals [12]. At the same time, the toxic effect of ATX-a on the morphofunctional state of the internal organs of warm-blooded animals remains poorly understood.

The aim of the research was to study morphofunctional changes in internal organs under the influence of ATX-a on the white rat bodies at intragastric intake in subchronic pilot experiments.

Material and methods

Experimental studies were carried out on conventional white male rats obtained from the nursery of the Andreevka Branch of the Federal State

Budgetary Institution of Science «Scientific Center for Biomedical Technologies» of the Federal Medical and Biological Agency in the amount of 40 pieces. The animals were kept in quarantine for 7 days before the start of the study. The animals were stratified by weight and randomized into groups relative to the dose. The control and experimental groups consisted of 10 males weighing 193 ± 19 g. Experimental doses of ATX-a in the amount of 0.01 µg/kg body weight, 0.1 µg/kg body weight and 1.0 µg/kg body weight for the subchronic experiment were selected taking into account the minimum LD_{50} and in accordance with MG 2.1.5.720–98*. ATX-a was administered intragastrically to laboratory animals daily for 90 days in the form of an aqueous solution of a certified reference sample ATX-a (made in the USA). The animals of the control group received water in equal volume. All work with animals was carried out in accordance with the principles set out in the Manual P 1.2.3156–13 [13]. At the end of the experiment, the animals of the control and experimental groups were euthanized using CO_2 .

Morphological, morphometric and stereometric research methods were used to identify morphofunctional changes in internal organs. The indicators were evaluated as a percentage (the number of indicators taken into account to the total number calculated) and in points (when an indicator was taken into account on an alternative basis or the degree of severity of the studied indicator was determined).

Internal organs were examined in each animal of the experimental and control groups: thyroid gland, thymus, heart, stomach (fundal part), liver (left lobe), spleen, pancreas (gastrointestinal part), ileum, colon, kidneys, adrenal glands, testes, according to [14]. Histological sections (5–10 µm thick) were prepared using a rotary microtome HM-325 with a slice transfer system (Microm, Germany). The sections were stained with hematoxylin-eosin according to the standard procedure on an automatic device Tissue-Tek DRS 2000 Sakura (Japan) and enclosed under a cover glass manually.

Morphological analysis of microscopic preparations was performed using the Vision Morpho system, consisting of: MT53001L microscope, Meiji Techno (Japan), digital video camera, computer with software. The indicators were evaluated as a percentage (the number of indicators taken into account to the total number calculated) and according to the severity of changes in points.

* Methodological Guidelines 2.1.5.720–98 “Substantiation of hygienic standards of chemicals in the water of water bodies for household and cultural water use” (approved by the Chief State Sanitary Doctor of the Russian Federation on October 15, 1998) Available at: <https://base.garant.ru/4175784/>

Table 1

Morphofunctional parameters in the stomach of animals of the control and experimental groups

Group	Violation of the boundaries between the mucosa and submucosa, point / increase in the sparsity of connective tissue fibers, point / puffiness, point	Hypersecretion of own glands, point / lipomatous inclusions in the submucosa, point	Increased infiltration, point / blood vessel filling, point
Control	$0,2 \pm 0,06 / 0,3 \pm 0,1 / 0,7 \pm 0,2$	$0,2 \pm 0,08 / 0,5 \pm 0,09$	$1,3 \pm 0,09 / 1,2 \pm 0,2$
II experiment (0.1 µg/kg b.w.)	$0,3 \pm 0,07 / 0,5 \pm 0,09 / 0,7 \pm 0,2$	$0 / 0,7 \pm 0,1$	$1,7 \pm 0,3 / 1,2 \pm 0,3$
III experiment (1 µg/kg b.w.)	$0,8 \pm 0,2^* / 0,8 \pm 0,2^* / 0,8 \pm 0,2$	$0,7 \pm 0,1^* / 0,5 \pm 0,1$	$1,5 \pm 0,2 / 1,3 \pm 0,3$

Note. Here and in Table 2–6: * – $p < 0,05$.

The data obtained were processed using descriptive statistics methods. The relative values (%) are presented as an average value and a standard deviation – $M \pm SD$. The normality of the distribution was checked according to the Shapiro–Wilk criterion. The differences between the control and experimental groups were determined by the Student's criterion (t). The reliability of the differences was considered statistically significant at $p < 0.05$. All the obtained research results were processed using the Statistica 10.0 software package [15–18].

Results

No spontaneous death of animals was observed throughout the experiment, and no significant differences in the appearance and behavior of animals in the control and experimental groups were noted.

As a result of the performed studies, it was found that in the stomach of rats exposed to ATX-a at a dose of 1 µg/kg of body weight (III experiment), there was a significant increase in hypersecretion of their own glands, an increase in violations of the boundaries between the mucosa and submucosa, an increase in the discharge of connective tissue fibers compared with the control. When the effective dose of ATX-a was reduced to 0.1 µg/kg (II experiment), no significant changes in the studied parameters were revealed compared with the control, which makes it possible to consider this dose inactive (Table 1).

In the colon, when exposed to ATX-a at a dose of 1 µg/kg of body weight, hypersecretion and blood vessel filling are statistically significantly increased. When the effective dose of ATX-a was reduced to 0.1 µg/kg (II experiment), no statistically significant changes in the studied parameters were revealed compared with the control, which allows us to consider this dose inactive (Table 2).

A number of changes in the endocrine glands have been detected. In the pancreas of rats, when exposed to ATX-a at a dose of 1 µg/kg of body weight (III experiment), there was a significant increase in fibrosis of the islets of Langerhans compared with

the control. When the effective dose was reduced to 0.1 µg/kg of body weight (II experiment), no statistically significant changes in the studied parameters were revealed compared with the control, which allows us to consider this dose inactive (Table 3).

A statistically significant increase in the proportion of lipomatous areas in the thymus compared with the control was revealed when exposed to a dose of ATX-a 1 µg/kg of body weight (Table 4).

Stereometric examination of the adrenal glands showed disorganization of the organ structure, characterized by a tendency to change the proportion of the cortical substance of the organ and the mesh zone in the cortical substance (Table 5). In the adrenal gland of rats, when exposed to ATX-a at doses of 1 µg/kg of body weight (III experiment) and 0.1 µg/kg of body weight (II experiment), disorganization of the organ structure was observed, characterized by a statistically significant increase in ectopia (displacement of cells or tissues to unusual places). When the effective dose of ATX-a was reduced to 0.01 µg/kg of body weight (I experiment), no statistically significant changes in the studied parameters were revealed (Table 5).

Table 6 presents the results of statistical processing of morphofunctional parameters of testes in animals of the control and experimental groups. In particular, a statistically significant increase in the number of spermatogenic cells was found in the tubules of the testes, compared with the control.

Table 2

Morphofunctional parameters in the colon in animals of the control and experimental groups, $M \pm m$

Group	Increased lymphoid infiltration, point / blood vessel filling, point / hypersecretion, point
Control	$1,5 \pm 0,2 / 0,5 \pm 0,2 / 0$
II experiment (0.1 µg/kg b.w.)	$1,8 \pm 0,1 / 0,7 \pm 0,2 / 0,2 \pm 0,1$
III опыт (1 мкг/кг м.т.)	$1,8 \pm 0,2 / 1,2 \pm 0,2^* / 1,2 \pm 0,3^*$

Table 3

Morphofunctional parameters in the pancreas in animals of the control and experimental groups, $M \pm m$

Group	Proportion of shares (%)			Destruction of the islets of Langerhans, % / their fibrosis, point	Edema, blood vessel filling, point
	exocrine part	islets of Langerhans	lipomatous areas		
Control	89,4 ± 8,4	7,5 ± 3,2	2,7 ± 1,4	1,2 ± 0,6 / 0,3 ± 0,1	1,3 ± 0,3
II experiment (0.1 µg/kg b.w.)	88,4 ± 8,3	11,3 ± 6,2	0,3 ± 0,2	1,3 ± (0,9–1,7) / 0,3 ± 0,1	1,5 ± 0,2
III experiment (1 µg/kg b.w.)	87,5 ± 8,8	11,0 ± 3,1	1,5 ± 0,3	1,2 ± (0,8–1,6) / 0,7 ± 0,15*	1,7 ± 0,3

Table 4

Morphofunctional parameters in the thymus in animals of the control and experimental groups, $M \pm m$

Group	The proportion of cortical matter, %	The proportion of cerebral matter, %	Lipomatous areas, point	The ratio of cortical and cerebral matter, point	Blood vessel filling, point / micronecrosis, point
Control	63,8 ± 8,3	36,0 ± 5,3	0,2 ± 0,1	2,2 ± 0,7	1,8 ± 0,6 / 0,2 ± 0,04
II experiment (0.1 µg/kg b.w.)	67,5 ± 7,8	32,5 ± 3,9	0	2,1 ± 1,1	1,7 ± 0,4 / 0,3 ± 0,07
III experiment (1 µg/kg b.w.)	64,5 ± 5,2	34,7 ± 2,5	0,8 ± 0,25*	2,1 ± 0,7	1,8 ± 0,5 / 0,3 ± 0,07

Table 5

Morphofunctional parameters in the adrenal gland in animals of the control and experimental groups, $M \pm m$

Group	The proportion of cortical matter, % / alteration of adrenocorticoocytes, in points	The proportion of cerebral matter, % / alteration of chromafin cells, point	The proportion of the mesh layer in the cortical substance, %	Ectopia of various cells of the cortical and cerebral matter, point	Formation of supr capsular tissue loci, point	Blood content in the cerebral matter, point / blood content in the cortical matter, point / lipomatous inclusions, point
Control	66,3 ± 3,3 / 0,5 ± 0,1	33,7 ± 7,3 / 0,5 ± 0,2	27,0 ± 3,3	0,8 ± 0,2	0	1,0 ± 0,3 / 1,0 ± 0,03 / 0
I experiment (0.01 µg/kg b.w.)	70,5 ± 4,5 / 0,5 ± 0,1	29,5 ± 3,5 / 0,8 ± 0,2	22,3 ± 1,9	1,3 ± 0,3	0	1,6 ± 0,5 / 0,8 ± 0,03 / 0
II experiment (0.1 µg/kg b.w.)	74,2 ± 6,5 / 1,0 ± 0,5	25,8 ± 4,2 / 0,8 ± 0,4	21,4 ± 2,4	2,6 ± 0,2*	0	1,2 ± 0,3 / 0,8 ± 0,04 / 0
III experiment (1 µg/kg b.w.)	68,2 ± 3,5 / 0,8 ± 0,3	31,8 ± 2,1 / 0,8 ± 0,2	28,7 ± 3,6	2,0 ± 0,3*	0	1,6 ± 0,3 / 0,7 ± 0,3 / 0

Table 6

Morphofunctional parameters in the testis in animals of the control and experimental groups, $M \pm m$

Group	Separation of the layers of spermatogenic cells from the basement membrane, point / increase in the number of spermatogenic cells in the tubules, point	The degree of discharge of spermatogenic cells in the seminal tubules		Interstitial edema, point / blood vessel filling, point / increase in the number of Leydig cells, point
		spermatogony, spermatocytes of the 1 st and 2 nd order, point	spermatids and spermatozoa, point	
Control	0,5 ± 0,1 / 0,3 ± 0,1	0,2 ± 0,06	0	0,8 ± 0,4 / 1,3 ± 0,7 / 0,5 ± 0,1
II experiment (0.1 µg/kg b.w.)	0,5 ± 0,1 / 0,2 ± 0,1	0,2 ± 0,08	0	0,5 ± 0,1 / 1,3 ± 0,9 / 0,3 ± 0,07
III experiment (1 µg/kg b.w.)	0,5 ± 0,1 / 0,8 ± 0,2*	0,2 ± 0,1	0	0,7 ± 0,3 / 1,2 ± 0,6 / 0,5 ± 0,1

Discussion

During the experiment, a different degree of sensitivity of the internal organs of warm-blooded animals to the effects of ATX-a was revealed. Morphofunctional changes were not detected in organs such as the heart, kidneys, liver, spleen, thyroid gland, which indicates the absence of pronounced effects of ATX-a in all tested doses.

At the same time, it was found that exposure to ATX-a at a dose of 1.0 µg/kg of body weight caused changes in a number of internal organs of white rats (experiment III) both stimulating (a 2.7-fold increase in the number of spermatogenic cells in the seminal tubules of the testes; a 3.5-fold increase in hypersecretion of the stomach's own glands; a 2.4-fold increase in hypersecretion in the large intestine) and disorganizing (the development of lipomatous sites in the thymus; an increase in the sparsity of connective tissue fibers in the stomach; fibrosis of the islets of Langerhans in the pancreas; ectopia of glandular tissue in the adrenal glands).

Morphofunctional changes in internal organs under the influence of ATX-a at a dose of 1.0 µg/kg of body weight in the digestive, reproductive and endocrine systems are consistent with the opinion of a number of researchers about their sensitivity, provided that toxic compounds enter the body orally [19, 20].

When reducing the dose of ATX-a to 0.1 µg/kg of body weight, there were no statistically significant differences in the morphofunctional state of internal organs in animals of the experimental group compared with the control, which makes it possible to consider this dose not effective according to the studied indicators.

The revealed ectopia of cells of the cortical and cerebral matter of the adrenal glands in experimental animals receiving a dose of 0.1 µg/kg of body weight, in the absence of significant morphofunctional differences with the control for all studied organs, provided that this indicator, according to some researchers, does not reflect the features of the mechanism of toxic effect of ATX-a on the animal body [19]. The revealed changes in ectopia in the adrenal gland when exposed to a dose of 0.1 µg/kg of body weight may be regarded as insignificant and require further research.

Conclusion

The revealed significant changes in morphological, morphometric and stereometric parameters when exposed to ATX-a at a dose of 1.0 µg/kg under conditions of subchronic intragastric intake in the absence of changes in animals receiving doses of 0.1 and 0.01 µg/kg confirm the previously established value of the threshold dose for general toxic effect at the level of 1.0 µg/kg body weight.

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