ISSN 2509-4327 (print)
ISSN 2510-4780 (online)

Deutscher Wissenschaftsherold
German Science Herald

№ 1/2021

Die Zeitschrift „Deutscher Wissenschaftsherold" ist eine Veröffentlichung mit dem Ziel ein breites Spektrum der Wissenschaft allgemeinverständlich darzustellen. Die Redaktionsleitung versteht sich als Vermittler zwischen Wissenschaftlern und Lesern. Durch die populärwissenschaftliche Bearbeitung wird es möglich unseren Lesern neue wissenschaftliche Leistungen am besten und vollständigsten zu vermitteln. Es werden Untersuchungen, Analysen, Vorlesungen, kurze Berichte und aktuelle Fragen der modernen Wissenschaft veröffentlicht.

Impressum
Deutscher Wissenschaftsherold – German Science Herald
Wissenschaftliche Zeitschrift
Herausgeber:
InterGING
Wiesenwinkel 2,
31785 Aerzen
Inhaber: Marina Kisiliuk
Tel.: + 49 5154 567 2017
Fax.: +49 5154 567 2018
Email: info@dwherold.de
Internet:www.dwherold.de
Chefredakeur:
Prof. Zamiatin P.M.
Korrektur:
O. Champela
Gestaltung:
N. Gavrilets

Auflage: № 1/2021 (Februari) – 20
Redaktionsschluss Februar, 2021
Erscheint vierteljährlich
Editorial office: InterGING
Wiesenwinkel 2,
31785 Aerzen
Tel.: + 49 5154 567 2017
Fax.: +49 5154 567 2018
Email: info@dwherold.de
Deutscher Wissenschaftsherold – German Science Herald is an international, German/English language, peer-reviewed journal and is published quarterly.
№ 1/2020
Passed in press in May, 2021
Druck: WIRmachenDRUCK GmbH
Mühlbachstr. 7
71522 Backnang
Deutschland

INDEXING: Index Copernicus, Google Scolar, Ulrich's Periodicals Directory, Fachzeitungen, MIAR.

http://miar.ub.edu/issn/2509-4327

DDC-UDC 591.481.4+616.314+616.379-008.64+612.06 DOI:10.19221/202116

Bilinskyi I.I.,
Assistant of the Department of Clinical Anatomy and Operative Surgery Ivano-Frankivsk National Medical University, Ukraine, ihor.bilinsk@ukr.net
Popovych Yu.I.,
Professor, Doctor of Medical Sciences (M.D.) of the Department of Clinical Anatomy and Operative Surgery Ivano-Frankivsk National Medical University, Ukraine, yupopovych@ifnmu.edu.ua
Fedorak V.M.
PhD of Medicine, Department of Clinical Anatomy and Operative Surgery, Ivano-Frankivsk National Medical University, Ukraine, fvm75@ukr.net

MORPHOLOGICAL CHANGES IN NEURONS OF THE INTRAMURAL DUODENAL APPARATUS IN CASE OF EXPERIMENTAL STREPTOZOTOCIN-INDUCED DIABETES MELLITUS AND STRESS

Abstract. *The article shows the study of morphological changes in neurons of the intramural nervous apparatus of the duodenum due to experimental diabetes mellitus and stress and in case of their combination. The experiment was carried out on 120 white sexually mature male rats. Material sampling was performed from the duodenum after 14, 28, and 56 days of the experiment. Morphological analysis of the state of nerve cells was carried out on preparations stained with 0.5% aqueous solution of cresyl violet according to the Nissl method, the detected changes in neurons were designated by scores and the degree of their changes was determined. It has been experimentally established that streptozotocin-induced diabetes mellitus leads to damage to the neural composition of the musculoskeletal plexus of the duodenum of rats, which is accompanied by the development of structural changes and the death of some neurons. As a result of immobilization stress, there is also a significant increase in the number of altered neurons and their degree of changes, which occurs due to destructive and dystrophic processes in the nerve cell. When these two conditions are combined, an increase in all morphological disorders and an increase in the number of atrophied and dead neurons is observed.*
Keywords: *duodenum, intramural nervous apparatus, experimental streptozotocin-induced diabetes mellitus, immobilization stress.*

According to WHO experts, 6-8% of the adult population suffers from diabetes mellitus (DM) and there is a growing trend. The number of patients with DM in the world in recent years is approximately 463 million people [1, 2, 3, 4]. One of the most common complications of DM is intestinal damage caused by prolonged glycemia and impaired innervation [5].

Many scientists have proven that DM is associated with changes in the size of neurons, a decrease in their quantitative composition, and neurodegenerative disorders [6, 7, 8]. Intestinal neurons are very vulnerable to hyperglycemia. DM leads to a decrease in their number, a decrease in neurotransmitter secretion, and neuroinflammation, resulting in destructive changes in nerve plexus cells: vacuolar dystrophy, axonal degeneration, necrosis, and apoptosis [1, 9].

One of the main factors that play a leading role in the development of pathologies of the gastrointestinal tract in humans is psychoemotional stress [10]. Today the problem of stress remains of high medical and social significance [11], it can activate the "intestinal-cerebral" axis through hormonal and neural pathways, which disrupts intestinal functions and causes significant changes in its neural composition.

Until now, the study of morphological features of the intramural duodenal apparatus in case of streptozotocin-induced DM under stress conditions has not been the subject of special studies. Thus, the analysis of domestic and foreign literature has shown that this issue is not fully studied and therefore it is topical to study

morphological changes in the nervous apparatus of the duodenum in case of experimental DM and stress, and their combination.

Objective of the study: to study morphological changes light-optically in neurons of the musculoskeletal plexus of the duodenum after 14, 28, 56 days of experimental streptozotocin-induced DM and stress, and in case of their combination.

Material and methods. The study was performed on 120 white mongrel sexually mature male rats divided into three groups: the first group – intact animals (15 rats); the second group – control (15 rats), which was administered 0.1 M citrate buffer in an equivalent dose intraperitoneally (at pH 4.5); the third group – experimental (90 rats), which includes three subgroups: 1 – with experimental DM (30 rats) modelled by a single intraperitoneal injection of streptozotocin (Sigma, USA) (60 mg/kg of body weight), diluted with 0.1 M citrate buffer; 2 – with chronic stress (30 rats) reproduced by placing animals in a closed plastic container according to the method described by H. V. Opanasenko; 3 – the combination of experimental DM and chronic stress (30 rats). It should be noted that studying and investigating all the results predicted in our work in animals of the control group, we did not find significant differences between the indicators in intact animals, so in the future, we took the data of animals of these two groups as a control.

Material sampling was performed from regions of the duodenum after 14, 28, and 56 days of the experiment. For histological examination of intramural neurons, pieces of the proximal and distal duodenum were fixed in 96% ethyl alcohol, the volume of which was 20 times the volume of the tissue, to a negative fat sample, and then carried out to paraffin blocks according to the generally accepted procedure. Sections with 5-8 µm thickness were made on a sledge microtome. Histological sections were stained according to the Nissl method with a 0.5% aqueous solution of cresyl violet.

The A.V. Svishchev's scheme was used to assess the state of nerve cells of the intramural apparatus of the duodenum. Morphological characteristics of the state of nerve cells and changes detected in them were designated by scores (tab. 1).

Using these indicators, the degree of changes (DC) of neurons in the musculoskeletal plexus was determined by the formula: DC = C×100/A, where C = 2b+2c+3d+4e+5f+6g+6h; A = a+C.

All manipulations that were carried out with animals during the experiment did not contradict the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986), European Council Directive 86/609/EEC (1986), the Law of Ukraine "On the Protection of Animals from Ill-Treatment" dated 15.12.2009 and Orders of the Ministry of Healthcare of Ukraine No. 690 dated 23.09.2009, No. 616 dated 03.08.2012. and met the requirements of the Ethics Commission of the Ivano-Frankivsk National Medical University (Protocol No. 104/18 dated 25.10.2018).

Table 1

Morphological characteristics of the state of neurons and their assessment in scores

Morphofunctional state of neurons	Scores	Conventional symbols
Unaltered	1	a
Hyperchromic	2	b
With the initial phenomena of swelling and chromatolysis	2	c
With the pronounced phenomena of swelling and chromatolysis	3	d
Vacuolated	4	e
Dehydrated	5	f
Atrophied	6	g
Dead	6	h

Results and discussion. After 14 days of experimental streptozotocin-induced DM, the structure of neurons in the musculoskeletal plexus of the duodenum undergoes significant changes. The number of morphologically altered neurons increases: in the proximal region – up to 42.00%, in the distal region – up to 40.50%, their number exceeds the control values by 2.05 times in the proximal part and 2.1 in the distal one (tab.2). The number of unaltered neurons is: in the proximal region – 58.8%, in the distal region – 59.50%. An

increase in the number of hyperchromic (6.00% and 5.50%) and vacuolated cells (3.00% and 2.50%) is found, neurons with vacuolization of peripheral parts of the cytoplasm are more common. In some nerve cells, vacuoles occupy a significant part of the cytoplasm. Also, the number of neurons with initial (20.00% in both parts) and pronounced (7.50% and 8.00%) phenomena of swelling and chromatolysis remains higher than the control values. There is an increased content of dehydrated (2.50% and 2.00%) and atrophied (1.50% and 2.00%) neurocytes of the musculoskeletal plexus of the duodenum compared to the control values. The death toll is (1.50% and 0.50%). The DC of neurons is higher than in the control group and is (66.86% and 64.90%).

An increased content of nerve cells of various morphological structures can be seen in all parts of the duodenum after 28 days of the experiment. Oval and rounded neurons predominate. There is a decrease in the number of altered neurons to 34.40% in the proximal region and 32.40% in the distal region, but the fairly high content of hyperchromic nerve cells remains (5.60% and 5.20%). The number of vacuolated nerve cells remains increased and is (2.40% and 3.20%), which is several times higher than the control values. The number of atrophied neurons remains high compared to the previous stage and significantly higher than in the control group (2.80% in both regions). Also, the content of dehydrated cells remains quite high (2.00% and 1.20%). There is a decrease in the number of neurons with initial (14.00% and 13.20%) and pronounced (6.80% and 6.40%) phenomena of swelling and chromatolysis compared to the previous stage. DC continues to be elevated by 60.58% in the proximal region and 56.17% in the distal region. The number of dead cells is lower compared to the previous stage and is (0.80% and 0.40%).

After 56 days of the experiment, the number of altered nerve cells in the musculoskeletal plexus of the duodenum decreases to 24.67% in the proximal region and 22.67% in the distal one. The fairly high content of vacuolated (2.67% in both regions) and dehydrated (1.33%, respectively)

Table 2

Distribution of neurons in the musculoskeletal plexus of the duodenum in the control and in case of DM.

Morpho-functional state of the neuron	Region	Intact	Control			DM		
			14	28	56	14	28	56
Unaltered	Pr	79.50	79.00	80.50	80.00	58.00	65.60	75.33
	D	81.00	80.00	81.00	79.50	59.50	67.60	77.33
Hyperchromic	Pr	4.00	3.50	4.00	4.00	6.00	5.60	3.33
	D	3.50	4.00	3.50	4.00	5.50	5.20	2.67
With the initial phenomena of swelling and chromatolysis	Pr	9.00	9.50	8.50	9.00	20.00	14.00	9.33
	D	8.50	9.00	8.50	9.00	20.00	13.20	10.00
With the pronounced phenomena of swelling and chromatolysis	Pr	5.00	5.00	5.00	4.50	7.50	6.80	4.67
	D	4.00	4.50	4.00	5.00	8.00	6.40	3.33
Vacuolated	Pr	1.00	1.50	1.00	1.50	3.00	2.40	2.67
	E	1.50	1.50	1.50	1.00	2.50	3.20	2.67
Dehydrated	Pr	0.50	0.50	0.50	0.50	2.50	2.00	1.33
	D	0.50	0.50	0.50	0.50	2.00	1.20	1.33
Atrophied	Pr	1.00	1.00	0.50	0.50	1.50	2.80	2.67
	D	1.00	0.50	1.00	1.00	2.00	2.80	2.00
Dead	Pr	0.00	0.00	0.00	0.00	1.50	0.80	0.67
	D	0.00	0.00	0.00	0.00	0.50	0.40	0.67
Total of the altered	Pr	20.50	21.00	19.50	20.00	42.00	34.40	24.67
	D	19.00	20.00	19.00	20.50	40.50	32.40	22.67
DC	Pr	40.23	41.26	38.08	38.93	66.86	60.58	50.44
	D	38.40	38.93	38.40	40.23	64.90	58.17	47.03

neurons remains, which exceeds several times the control data. A decrease in the number of cells is observed with initial (9.33% and 10.00%) and pronounced (4.67% and 3.33%) phenomena of swelling and chromatolysis compared to the previous stage. In light-optical microscopy, the nuclei are enlarged in size and shifted to the periphery, and they are illuminated. Tigroid grains are unevenly distributed in neuroplasma. They form clusters along the periphery of the perikaryon, while chromatolysis is sometimes seen around the nuclei. The number of hyperchromic neurons also decreases (3.33% and 2.67%), but later atrophied (2.67% and 2.00%) and single dead neurons (0.67% in both regions) are observed, near which an accumulation of gliocytes is found. DC decreases comparatively to the previous stage (50.44% and 47.03%) but remains high in comparison to the control.

In the early stages of development of streptozotocin-induced DM, compensatory and adaptive processes are observed in response to hyperglycemia: an increase in the area of neurons and their nuclei, an increase in the volume density of neurosecretory granules in them. At a later stage of experimental DM, dystrophic-destructive changes are observed, which lead to a decrease in the functional activity of neurons [6, 8, 9].

Experimental streptozotocin-induced DM leads to significant damage to neurons of the musculoskeletal plexus of the duodenum of rats, an increase in the number of morphologically altered neurons and the degree of their changes, which is accompanied by structural disorders and the death of some neurons.

After 14 days of immobilization stress, the neurons of the musculoskeletal plexus of the duodenum undergo significant morphological changes. The percentage of unaltered nerve cells is 52.00% in the proximal region and 54.00% in the distal region (tab.3). The number of altered neurons exceeds the control values by about 2 times and is slightly higher than in DM, and is equal to (48.00% and 46.00%). This stage of the experiment is characterized by a significant increase in hyperchromic (8.00% and 4.00%), vacuolated (6.00% in both regions) and dehydrated (2.00% in both regions) nerve cells. The content of cells with initial (20.00% and 18.00%) and pronounced (8.00% and 14.00%) phenomena of swelling and chromatolysis remains quite high. During this stage, dystrophic processes are detected in the form of pericellular edema, wrinkling of single neurons, which manifests itself in the form of the sinking of the lateral and basal surfaces. Neurocyte nuclei become elongated rod-shaped, and sometimes hyperchromia phenomena are observed. There are also atrophied (2.00% in both regions) and single dead (2.00% and 1.00%) neurocytes. DC is (72.63% and 70.97%), which exceeds the control data by several times and remains higher than in case of DM.

On day 28 of stress, the number of altered neurons decreases to 36.80% in the proximal and up to 35.60% in the distal regions compared to the previous stage but remains higher than the control values. Further, the fairly high content of vacuolated (4.80% and 4.40%) and dehydrated (2.40 in both regions) nerve cells remains. At this time there is acute edema of neurons, an increase in the size of the nucleus and cytoplasm, ectopia of the nucleus and nucleoli, lysis of the basophilic substance. Cells with hyperchromia are often detected (5.20% and 4.80%), their number decreases compared to the previous stage. The content of neurocytes with initial (13.60% and 13.20%) and pronounced (6.40% and 6.80%) phenomena of swelling and chromatolysis remains high compared to the control data but is less than after 14 days of the experiment. The percentage of the atrophied also increases compared to the previous stage and amounts to (3.20% and 2.80%), there are single dead nerve cells. DC is (64.41% and 63.07%) and remains higher compared to the control and DM.

After 56 days of immobilization stress, there is a further decrease in the number of altered nerve cells to (30.80% and 29.20%). The percentage of neurons with initial and pronounced phenomena of swelling and chromatolysis also decreases compared to the previous stages but remains slightly higher than in the control. During this stage, hyperchromic (4.80% and 4.40%), vacuolated (3.20% and 3.20%) and dehydrated (1.20% and 1.20%) neurocytes occur. The number of atrophied and dead cells remains unchanged compared to the previous stage but slightly increased compared to the control values. DC is (57.49% and 55.53%).

Table 3

Distribution of neurons in the musculoskeletal plexus of the duodenum in case of chronic stress.

Morpho-functional state of the neuron	Region	Intact	Control			Stress		
			14	28	56	14	28	56
Unaltered	Pr	79.50	79.00	80.50	80.00	52.00	63.20	69.20
	D	81.00	80.00	81.00	79.50	54.00	64.40	70.80
Hyperchromic	Pr	4.00	3.50	4.00	4.00	8.00	5.20	4.80
	D	3.50	4.00	3.50	4.00	4.00	4.80	4.40
With the initial phenomena of swelling and chromatolysis	Pr	9.00	9.50	8.50	9.00	20.00	13.60	11.60
	D	8.50	9.00	8.50	9.00	18.00	13.20	11.20
With the pronounced phenomena of swelling and chromatolysis	Pr	5.00	5.00	5.00	4.50	8.00	6.40	6.00
	D	4.00	4.50	4.00	5.00	14.00	6.80	5.60
Vacuolated	Pr	1.00	1.50	1.00	1.50	6.00	4.80	3.20
	D	1.50	1.50	1.50	1.00	6.00	4.40	3.20
Dehydrated	Pr	0.50	0.50	0.50	0.50	2.00	2.40	1.20
	D	0.50	0.50	0.50	0.50	2.00	2.40	1.20
Atrophied	Pr	1.00	1.00	0.50	0.50	2.00	3.20	2.80
	D	1.00	0.50	1.00	1.00	2.00	2.80	3.20
Dead	Pr	0.00	0.00	0.00	0.00	2.00	1.20	1.20
	D	0.00	0.00	0.00	0.00	0.00	1.20	0.40
Total of the altered	Pr	20.50	21.00	19.50	20.00	48.00	36.80	30.80
	D	19.00	20.00	19.00	20.50	46.00	35.60	29.20
DC	Pr	40.23	41.26	38.08	38.93	72.63	64.41	57.49
	D	38.40	38.93	38.40	40.23	70.97	63.07	55.53

Consequently, due to immobilization chronic stress, there is an increase in the number of morphologically altered neurons and the degree of their changes, which is accompanied by swelling of individual neurons, the development of destructive disorders and the death of their part.

The increased content of morphologically altered neurons (51.20% and 50.00%) was observed in the musculoskeletal plexus of the duodenum after 14 days of the combination of experimental DM and stress compared to other experimental groups (tab. 4). The number of nerve cells with initial (22.00 and 22.40%) and pronounced (10.80% and 11.60%) phenomena of swelling and chromatolysis is several times higher than the control values. There is a high level of hyperchromic (5.20% and 4.80%), vacuolated (5.60% and 4.40%) and dehydrating (3.60 in both regions) neurons. The percentage of atrophied neurocytes is equal to (2.00% and 1.60%), there is an increase in dead cells (1.60% and 1.20%). DC is (75.60% and 74.23%) and remains higher compared to the control and the other two groups.

After 28 days of the experiment, the percentage of unaltered neurons is 53.00% in the proximal region and 56.00% in the distal one. The number of altered nerve cells (47.00% and 44.00%) exceeds the control values by about two times but decreases in comparison to the previous stage. A decrease in the vacuolated (5.00% and 4.00%) and dehydrated (3.00% and 4.00%) is observed, but the fairly high content of cells remains with initial (21.00% and 19.00%) and pronounced (19.00% and 10.00%) phenomena of swelling and chromatolysis. Individual hyperchromic cells are found. The degree of changes in neurons is less than in the previous stage but remains high compared to the control values. The number of atrophied neurons increases and is equal to (3.00% in both regions). The number of dead cells continues to rise to (2.00% and 1.00%).

After 56 days of the experiment, a further decrease in altered neurons is observed in the duodenal nerve plexus to 40.00% in the proximal region and up to 38.40% in the distal region compared to the previous terms. The number of unaltered neurons is (60.00% and 61.60%). The number of hyperchromic (4.80% and 5.20%), vacuolated (4.80% and 5.20%) and dehydrated (2.40% and 2.00%) nerve cells remains slightly increased. The number of neurons decreases with initial (16.40% and 16.80%) and pronounced (7.20% and 7.60%) phenomena of swelling and chromatolysis. The percentage of atrophied neurocytes remains increased compared to the previous stage and significantly higher than in the control group (3.20 in both regions). The death toll is reduced to (1.20% and 0.80%). The degree of changes is (66.96% and 64.52%) and remains the highest than in other experimental groups.

Table 4

Distribution of neurons in the musculoskeletal plexus of the duodenum in case of a combination of DM and stress

Morpho-functional state of the neuron	Region	Intact	Control			DM+stress		
			14	28	56	14	28	56
Unaltered	Pr	79.50	79.00	80.50	80.00	48.80	53.00	60.00
	D	81.00	80.00	81.00	79.50	50.00	56.00	61.60
Hyperchromic	Pr	4.00	3.50	4.00	4.00	5.20	3.00	4.80
	D	3.50	4.00	3.50	4.00	4.80	3.00	5.20
With the initial phenomena of swelling and chromatolysis	Pr	9.00	9.50	8.50	9.00	22.00	21.00	16.40
	D	8.50	9.00	8.50	9.00	22.40	19.00	16.80
With the pronounced phenomena of swelling and chromatolysis	Pr	5.00	5.00	5.00	4.50	10.80	10.00	7.20
	D	4.00	4.50	4.00	5.00	11.60	10.00	7.60
Vacuolated	Pr	1.00	1.50	1.00	1.50	5.60	5.00	4.80
	D	1.50	1.50	1.50	1.00	4.40	4.00	2.80
Dehydrated	Pr	0.50	0.50	0.50	0.50	3.60	3.00	2.40
	D	0.50	0.50	0.50	0.50	3.60	4.00	2.00
Atrophied	Pr	1.00	1.00	0.50	0.50	2.40	3.00	3.20
	D	1.00	0.50	1.00	1.00	2.00	3.00	3.20
Dead	Pr	0.00	0.00	0.00	0.00	1.60	2.00	1.20
	D	0.00	0.00	0.00	0.00	1.20	1.00	0.80
Total of the altered	Pr	20.50	21.00	19.50	20.00	51.20	47.00	40.00
	D	19.00	20.00	19.00	20.50	50.00	44.00	38.40
DC	Pr	40.23	41.26	38.08	38.93	75.60	72.96	66.96
	D	38.40	38.93	38.40	40.23	74.23	70.53	64.52

With a combination of DM and stress, a significant increase in the development of destructive and dystrophic processes is observed in the musculoskeletal plexus of the duodenum, which is accompanied by an increase in the number of morphologically altered neurons and the degree of their changes and leads to atrophy and death of some nerve cells.

Conclusions. 1. When analyzing the morphological state of duodenal neurons, we found that after 14-56 days of streptozotocin-induced DM, the number of transformed neurons increases, the number of which reaches its maximum on the 14th day of the experiment. The content of cells with initial and pronounced phenomena of swelling and chromatolysis increases, the share of dehydrated and vacuolated nerve cells increases significantly, which leads to atrophy and death of neurons. So, in case of DM, reactive-dystrophic changes predominate in the musculoskeletal plexus of the duodenum, accompanied by functional tension of structures.

2. After 14-56 days of immobilization stress, we found significant changes in the nervous composition of the musculoskeletal plexus of the duodenum, namely: an increase in the number of cells with initial and pronounced phenomena of swelling and chromatolysis, an increase in the number of hyperchromic, vacuolated and dehydrated neurons, which leads to destructive and dystrophic changes, atrophy and their death. Such morphological features of neuronal rearrangement indicate their high functional activity, which is associated with polyphagia and constant intestinal motility for evacuation of food masses.

3. After 14-56 days of streptozotocin-induced DM in combination with stress, a significant increase in structural damage to neurons of the musculoskeletal plexus of the duodenum has been found. There is a high percentage of cells with initial and pronounced phenomena of swelling and chromatolysis, an increase in the number of vacuolated and dehydrated nerve cells, which leads to an increase in destructive changes and their death.

Prospects for further research. It is promising to use morphometric analysis of metric indicators of neurons, which will enable us to understand better the patterns of changes in duodenal neurons and the role of its intramural nervous apparatus in the development of compensatory and recovery processes in experimental DM, chronic stress and their combination.

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